Draft Comparative Effectiveness Review

Number XX

The Effectiveness of Indoor Allergen Reduction and the Role of Bronchial Thermoplasty in the Management of Asthma

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No.
To be added to final report.

Prepared by:
To be added to final report.

Investigators:
To be added to final report.

AHRQ Publication No. xx-EHCxxx
<Month Year>

Purpose of Review

To evaluate the effectiveness of indoor allergen reduction interventions, and bronchial thermoplasty, on asthma outcomes.

Key Messages

- Single interventions designed to reduce indoor allergen exposure may have little effect on asthma outcomes.
- Multicomponent interventions that bundle more than one strategy may improve some asthma outcomes, but it is unclear which components are most important.
- The evidence base for both single and multicomponent interventions is insufficient for addressing many primary outcomes.
- Bronchial thermoplasty may reduce exacerbations and improve pulmonary function with a low frequency of serious adverse events.

This report is based on research conducted by an Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. xxx-xxxx-xxxxx). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov.

Suggested citation: *To be added to final report.*

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The National Heart, Lung, and Blood Institute (NHLBI), one of the National Institutes of Health (NIH), requested that AHRQ conduct a systematic review of the questions and provided funding for this.

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

Sharon Arnold, Ph.D.
Acting Director
Agency for Healthcare Research and Quality

Arlene Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Aysegul Gozu, M.D., M.P.H., FACP
David W. Niebuhr, M.D., M.P.H., M.Sc.
Task Order Officers
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Acknowledgments

To be added to final report.

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report follows:
To be added to final report.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers follows:
To be added to final report.

The Effectiveness of Indoor Allergen Reduction and the Role of Bronchial Thermoplasty in the Management of Asthma

Structured Abstract

Objectives. This review evaluates the effectiveness of allergen reduction interventions on asthma outcomes in adults and children. The review also assesses the role of bronchial thermoplasty (BT) in adults with severe asthma.

Data sources. We systematically searched the gray literature and five bibliographic databases: MEDLINE, EMBASE, PubMed, CINAHL, and the Cochrane Library through November 3, 2016, for allergen reduction interventions and through June 22, 2016, for BT.

Review methods. Eligible studies included systematic reviews, meta-analyses, randomized controlled trials (RCTs), and nonrandomized interventional studies. For BT, case reports and series describing adverse events were also considered. Studies were evaluated for risk of bias using the Cochrane Risk of Bias instrument or the Newcastle-Ottawa scale, and the evidence base was assessed using a GRADE approach.

Results. Our literature searches identified 68 publications of interventions to reduce exposure to indoor allergens and their effects on asthma. This included 57 unique trials with data published in 61 articles and seven nonrandomized controlled studies. Validated measures of asthma control were infrequently reported across studies, and findings were often inconclusive. Twenty-eight studies evaluated single interventions. Use of acaricides (dust mite pesticides) did not improve pulmonary function (Low SOE). Air purification devices, used alone, improved quality of life (Low SOE), but did not reduce healthcare utilization (Low SOE). Impermeable mattress covers did not reduce exacerbations or medication use, or improve quality of life (all High SOE). Carpet removal, high-energy particulate air (HEPA) filtration vacuums, mold removal, pest control, and pet removal were not adequately examined by single intervention studies. Twenty-nine studies assessed multicomponent interventions, but wide differences among study interventions (and combinations of interventions) precluded meta-analysis. When examined as a component within a broader set of interventions, use of air purification reduced school absenteeism (Low SOE) but did not reduce exacerbations (Moderate SOE) or improve quality of life (Moderate SOE). HEPA vacuums, when included in a multicomponent approach, reduced exacerbations and improved quality of life (Moderate SOE) for children. Mattress covers used within multicomponent interventions reduced school absenteeism and missed activities (Low SOE) but had no effect on emergency department visits (Low SOE), hospitalizations (High SOE), and quality of life (Moderate SOE). Pest control strategies incorporated into multicomponent interventions reduced exacerbations (Moderate SOE), improved quality of life (Low SOE) and reduced school absenteeism (Low SOE), but did not reduce acute care clinic visits (High SOE) or worker absenteeism (Low SOE). Carpet removal, mold removal, and pet removal were included within multicomponent interventions, but the evidence for these strategies was inconclusive.

Fifteen studies, including three RCTs with 5-year follow up, examined the impact of BT on patients with moderate to severe asthma, who also had fewer than three exacerbations within the

past year or who did not use high doses of oral corticosteroids. BT and medical management improved asthma control, FEV_1, and quality of life more than medical management alone, but did not reduce healthcare utilization (low SOE). BT compared to sham control did not improve asthma control, but BT reduced exacerbations, improved FEV_1, and improved quality of life (Low SOE). Common adverse events following BT included bronchial irritation, chest discomfort, cough, discolored sputum, dyspnea, night awakenings, and wheezing. Severe adverse events including collapsed lung lobes, hemoptysis, chest infections, and pleurisy were reported. in five case reports and two small case series. No deaths were attributed to BT.

Conclusions. Single intervention studies showed almost no benefit, with only one study of air purification devices resulting in improved quality of life, while most studies showed no effect or had inconclusive results. Multicomponent interventions may be more valuable, with studies showing improvement in various outcomes when using combinations of interventions such as air purification devices, HEPA vacuums, mattress covers, and pest control strategies. BT improved FEV1 and quality of life while reducing exacerbations. Serious adverse events were infrequent. The available body of literature on BT is small, however, and the generalizability of the findings to patients with severe asthma and multiple comorbidities is limited.

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Introduction

Background

Asthma is a chronic inflammatory disorder of the airways, characterized by varying degrees of airflow obstruction. Bronchoconstriction, inflammatory cell infiltration, and airway edema reduce airflow intermittently, often in response to specific exposures, resulting in respiratory symptoms.[1] In the United States, asthma's prevalence has increased over the past decade, from an estimated 22.2 million Americans in 2005 to 24 million Americans in 2014.[2,3] Asthma can significantly affect patients' and families' quality of life and ability to pursue activities such as school, work, and exercise. Globally, asthma ranks 14th based on the burden of disease, as measured by disability-adjusted life years.[4] In the United States, asthma contributes significantly to health care resource utilization and associated costs. For example, in 2012, asthma was one of the top 20 leading diagnosis groups for primary care visits and was the main reason for 1.8 million emergency department visits and 439,000 hospitalizations. While the severity of disease varies between patients and over time in the same patient, asthma can be fatal, accounting for approximately 1 death per 100,000 Americans.[5]

Effectiveness of Indoor Inhalant Allergen Reduction

Control of environmental factors that may contribute to asthma is one of the four components of asthma management. Many common indoor inhalant allergens have been associated with increased risk of asthma exacerbations, including pollen, animal dander, house dust mites (HDMs), mice, cockroaches, mold, and others.[6] Numerous interventions have been designed to reduce exposure to allergens in the environment where patients with asthma live, work, learn, play, and sleep.[7] Examples of these interventions include use of acaricides (HDM pesticides), air purification systems, carpet removal or vacuuming, use of specially designed mattress covers and pillowcases, mold removal, pest control techniques, and containment or removal of family pets.

Evaluating the effectiveness of allergen exposure reduction interventions presents multiple challenges. Strategies to control environmental factors often include multicomponent approaches, which incorporate at least two different interventions resulting in difficulty identifying the effectiveness of individual component interventions. Similarly, some interventions are designed to reduce or eradicate exposure to multiple allergens simultaneously, and the data for individual allergens varies. Other challenges in interpreting the literature include inadequate or inconsistent measures of allergen exposure, inadequate documentation of subjects' sensitization to the allergen targeted for removal, and heterogeneity within specific interventions (e.g., devices used for air filtration vary).

Role of Bronchial Thermoplasty in the Management of Asthma

In addition to removing relevant environmental triggers, patients with severe, persistent asthma are managed with multiple medications that may include inhaled, orally administered, and biologic therapeutics. For some of these patients, bronchial thermoplasty (BT) is another treatment option, which requires three bronchoscopies performed by a physician. Bronchoscopy is used to visualize the airway before applying a catheter to the airway wall to deliver heat. The thermal energy is intended to reduce excess smooth muscle in the treated airways.[8] In April 2010, the U.S. Food and Drug Administration (FDA) approved the Alair BT system for use in patients 18 years of age or older with severe, persistent asthma.

Purpose of the Systematic Review

In 1989, the National Heart, Lung, and Blood Institute (NHLBI) initiated the National Asthma Education and Prevention Program (NAEPP) to address growing concern about asthma in the United States. One of the NAEPP's first accomplishments was to convene a panel of experts who produced a report in 1991, *The National Asthma Education and Prevention Program Expert Panel Report (EPR): Guidelines for the Diagnosis and Management of Asthma*. The guidelines address the diagnosis, evaluation, and treatment of asthma. Given that the most recent report, EPR-3, was published in 2007,[1] NHLBI assessed the need for an update by requesting information from the public, NAEPP Coordinating Committee Members and its affiliates, and members of the 2007 Expert Panel. Collected information was provided to the NHLBI Advisory Council Asthma Expert Working Group, which produced a report to summarize the process and recommendations from their needs assessment.[9] The Working Group identified six high-priority topics that should be updated. For each topic, key questions meriting a systematic literature review were formulated. NHLBI engaged AHRQ to perform the systematic reviews through its Evidence-based Practice Centers (EPCs). This document represents the systematic review of "The Effectiveness of Indoor Allergen Reduction and the Role of Bronchial Thermoplasty in the Management of Asthma." The review also highlights areas of controversy and identifies needs for future research on these priority areas.

Scope and Key Questions

This report's main objective is to conduct a systematic review of the benefits and harms of nonpharmacologic interventions for the management of asthma in adults and children. In this review, we address the following key questions (KQs):

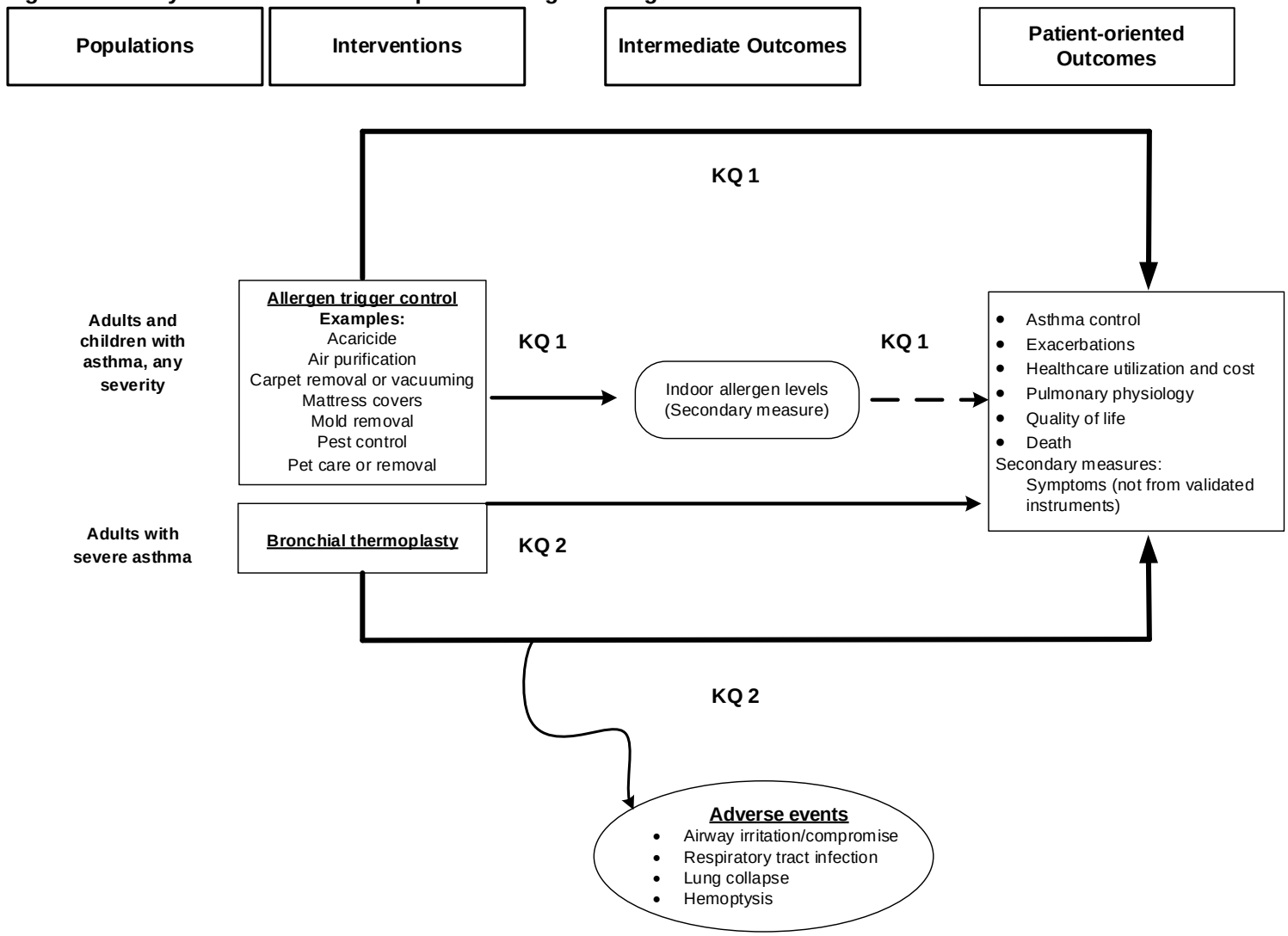
Key Question 1: Among individuals with asthma, what is the effectiveness of interventions to reduce or remove exposure to indoor inhalant allergens on asthma control, exacerbations, quality of life, and other relevant outcomes?

Key Question 2: What are benefits and harms of using BT in the treatment of adult (>18 years) patients with severe asthma in addition to standard treatment?

Analytic Framework

We developed an analytic framework to guide the systematic review process (Figure 1).

Figure 1. Analytic framework for nonpharmacologic management of asthma



KQ=key question
Dashed line indicates theoretical relationship

Organization of This Report

In the remaining three chapters of this report, we describe the methods for this systematic review, present the results for each KQ, and discuss the overall findings. Within the Results chapter, we provide the results of the literature searches and screening procedures, as well as descriptions of included studies, key points, detailed syntheses of the studies, and strength-of-evidence tables for each KQ. The Discussion chapter reviews the key findings and strength of evidence for each KQ, places the findings in the context of previous systematic reviews, examines the general applicability of the studies, discusses implications for decisionmaking, describes limitations of the systematic review process and the evidence base for each KQ, and identifies knowledge gaps that require further research.

A list of acronyms and abbreviations appears after the references, followed by three appendixes. The Appendixes include Appendix A. Search Strategy, Appendix B. Excluded Studies, and Appendix C. Evidence Tables.

Methods

Topic Refinement and Review Protocol

National Heart, Lung, and Blood Institute (NHLBI) initially nominated this topic, as described in the Introduction. We generated an analytic framework, preliminary Key Questions (KQ), and preliminary inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, timing, and settings). These processes were guided by information provided by the topic nominator. A Technical Expert Panel (TEP) was convened for this report. The TEP consisted of nine scientists and clinicians, including individuals with expertise in the clinical management of pediatric and adult asthma, implementation of environmental control interventions to reduce exposure to allergens in the home, and the use of bronchial thermoplasty (BT). TEP members participated in conference calls and discussions through e-mail to review the scope, analytic framework, KQs, and PICOTS and provided input on the information and categories included in evidence tables and the analysis. A list of the TEP members will be included in the front matter of the final report. We drafted a protocol for developing this systematic review and finalized it in consultation with the Agency for Healthcare Research and Quality (AHRQ) and NHLBI before it was posted on the Effective Health Care Web site on October 11, 2016. A full version of our protocol for this systematic review is available online (https://effectivehealthcare.ahrq.gov/ehc/products/643/2318/asthma-nonpharmacologic-treatment-protocol-161004.pdf),[10] and is registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO) registration number CRD42017055547).[11]

Literature Search Strategy

Search Strategy

Literature searches were performed by Medical Librarians at the Evidence-based Practice Center (EPC) Information Center and followed established systematic review protocols. Searches covered the literature published from database inception (dates vary, see Appendix A) through November 3, 2016, for KQ 1 and through June 22, 2016, for KQ 2.

We searched the following databases using controlled vocabulary and text words: EMBASE and MEDLINE (searched together on the EMBASE.com platform), PubMed (In Process citations), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and the Cochrane Library.

We used text words to search gray literature sources and the Web sites of relevant organizations identified by the clinical experts on the project team. A complete list of the resources we searched is available in Appendix A.

Search resources, concepts, and strategies are available in Appendix A. Reference lists from systematic reviews and meta-analyses were reviewed and compared against our retrieved articles. If a systematic review contained references that appeared to meet our inclusion criteria, but had not been captured by our initial search results, the search strategy was refined to include these articles. Scientific Information Packets submitted by interested parties were also reviewed.

Literature screening was performed in duplicate using the database Distiller SR (Evidence Partners, Ottawa, Ontario, Canada). Literature search results were initially screened for relevancy. Relevant abstracts were screened against the inclusion and exclusion criteria in duplicate. Studies that appeared to meet the inclusion criteria were retrieved in full and screened

again in duplicate against the inclusion and exclusion criteria. All disagreements were resolved by consensus discussion between the two original screeners. The literature searches will be updated during the Peer-Review process before finalization of the review.

Inclusion and Exclusion Criteria

Publication Criteria

Included articles must have been published as full-length, peer-reviewed studies. Abstracts and meeting presentations were not included because they do not include sufficient details about experimental methods to permit an evaluation of study design and conduct; they may also contain only a subset of measured outcomes.[12,13] Additionally, it is not uncommon for abstracts that are published as part of conference proceedings to have inconsistencies compared with the final study publication or to describe studies that are never published as full articles.[14-18] To avoid double-counting patients, when several reports of the same or overlapping groups of patients were available, only outcome data from the report with the most patients were included. However, we included data from a smaller study when it either reported data on an outcome that the index report did not provide or when it provided longer followup data for a specific outcome.

English language: When a study with an English abstract but published in a foreign language was identified, the abstract was assessed against the full set of inclusion/exclusion criteria. If the study appeared to fit the inclusion criteria, we evaluated whether excluding the study might result in language bias (e.g., if the findings differ from other included studies.) If language bias seemed unlikely, the study was excluded.

Study Selection

We followed the PICOTS (Table 1) framework in developing the criteria for inclusion of studies. We included studies of patients of any age with a diagnosis of allergic asthma. We included studies of asthma and other allergic conditions, when ≥85 percent of enrolled patients had asthma or when outcomes were reported separately for the subgroup with asthma. Studies had to report on the outcomes pre-specified in our PICOTS. Study inclusion was not restricted by language of publication or treatment duration. Randomized controlled trials (RCTs), and nonrandomized interventional studies with concurrent controls (e.g., nonrandomized trials) or historical controls (e.g., pre-post studies) were considered for inclusion for all KQs. Case reports or case series that describe adverse events associated with BT were considered for inclusion for KQ 2. *In vivo, in vitro*, and animal studies were excluded.

Table 1. PICOTS (populations, interventions, comparisons, outcomes, timing, and setting) criteria for including studies in the review

Populations	**Key Question 1** • All severity of asthma • Any age **Key Question 2** • Severe asthma • ≥18 years
Interventions	**Key Question 1** • Acaricide (house dust mite pesticide) o Applied to carpet, mattresses, and/or furniture • Air quality o Air purifiers o Ventilation or duct cleaning • Carpet o Removal o Wall-to-wall versus area rugs o Cleaning (professional services; high efficiency particulate air filtration (HEPA) vacuums) • Linens and furniture o Pillow/mattress covers o Furniture covers/"wipe-down" furniture o Frequent laundering of linens • Mold removal • Animals and insects o Pet bathing o Pet removal or restriction of pet access o Pest control (professional and lay interventions) • Multicomponent interventions o Multiple strategies implemented concurrently **Key Question 2** • Bronchial thermoplasty
Comparators	**Key Question 1** • No intervention to reduce or eliminate exposure to indoor inhalant allergen(s) • Reduction or elimination of exposure to different indoor inhalant allergen(s) • Reduction or elimination of exposure to multiple indoor inhalant allergens **Key Question 2** • Treatments used in patients with severe asthma excluding thermoplasty

Table 1. PICOTS (populations, interventions, comparisons, outcomes, timing, and setting) criteria for including studies in the review (continued)

Outcomes	**Primary Outcomes, All Key Questions**
	• Asthma control
	  o Asthma Control Test (ACT) / Childhood ACT
	  o Asthma Control Questionnaire (ACQ)
	• Exacerbations
	  o Systemic corticosteroids for asthma
	  o Asthma-specific hospitalizations
	  o Asthma-specific ED visits
	  o Asthma-specific urgent care visits (other than ED)
	  o Asthma-specific admissions to intensive care unit, or intubations
	• Health care utilization and costs
	  o Asthma-specific ambulatory care visits
	  o Asthma-specific medication use (including medication name, dose, duration)
	  o Hospitalizations, ED visits, urgent care visits
	  ▪ All cause
	  ▪ Associated with potentially asthma-related complications
	  □ Pneumonia
	  □ Myocardial infarction
	  □ Steroid-induced hypoglycemia
	  o Asthma-specific days missed from work or school
	  o Participation in sports and recreational activities
	• Pulmonary physiology
	  o Peak expiratory flow
	  o Spirometry
	  o Airway hyper-responsiveness
	• Quality of life
	  o Asthma Quality of Life Questionnaire (AQLQ)
	  o Pediatric Asthma Quality of Life Questionnaire (PAQLQ)
	  o Pediatric Asthma Caregivers Asthma Quality of Life Questionnaire (PACQLQ)
	• Death, asthma-specific and all cause
	Secondary Measures, Key Question 1
	• Patient-reported symptoms
	• Indoor inhalant allergen levels measured by formal testing
	Adverse events, Key Question 2
	• Patient-reported airway irritation (cough, wheezing, dyspnea, chest discomfort)
	• Airway compromise
	• Upper or lower respiratory tract infections
	• Lung collapse
	• Hemoptysis

Timing	Studies with all lengths of followup duration will be considered
Setting	**Key Question 1** • Home • Work • School • Daycare **Key Question 2** • Clinical settings

Data Extraction

Data were abstracted using Microsoft Word. Duplicate abstraction on a 10-percent random sample was used to ensure accuracy. All discrepancies were resolved by consensus discussion among the two original abstracters and an additional third person as needed. Elements abstracted included general study characteristics, patient characteristics, details of interventions, outcomes data, and risk of bias items.

Risk of Bias Assessment of Individual Studies

We used the Cochrane Collaboration's tool for assessing risk of bias in RCTs.[19] Study characteristics were rated as introducing "Low," "High," or "Unclear" risk of bias. For nonrandomized studies, we used the Newcastle-Ottawa scale and rated as "Low," "Moderate," "High," or "Unclear."[20] Risk of bias was assessed by two independent reviewers, and discrepancies were addressed through consensus discussion.

We considered the funding source of individual studies as presenting a potentially important risk of bias. Therefore, for any study that reported receiving all or part of its funding from, or was coauthored by one or more employees of a commercial manufacturer of an intervention, we noted that information in the Risk of Bias tables. We also rated the "Other Sources of Bias" component in the Cochrane scale as "High" in cases where study funding presented a potential conflict of interest.

Data Synthesis

Due to the heterogeneity of the included studies, we did not attempt to combine data from the studies quantitatively using meta-analyses. Additionally, some interventions were evaluated in only one study; thus, quantitative synthesis was not possible. Instead, we provide a narrative synthesis of the studies' general findings.

For the multicomponent studies, we organized the data synthesis and analysis by grouping studies according to their active components. We defined the "active component" as an intervention that was implemented in the intervention arm but not the control arm of a study. Such interventions met inclusion criteria of this review as shown in Table 1 above.

We have described outcomes as statistically significant when identified as such by the authors of the primary studies. Statistical significance, however, does not always equate with clinically significant changes in outcomes. In the Strength of Evidence tables, we noted any cases where a statistically significant result was not associated with an absolute difference of at least ten percent (between groups or above baseline, depending on the comparison), for the critical outcomes.

Critical outcomes for all KQs included the following validated outcomes: asthma-control measures, asthma-exacerbation measures, asthma-related healthcare utilization and costs, asthma-related pulmonary physiology, and asthma-related quality of life. They also included the secondary measures of symptoms and allergen levels. In addition, for KQ 2, we also considered adverse events as critical outcomes.

Strength of the Body of Evidence

For questions with clinical outcomes, we graded the strength of evidence (SOE) based on the guidance established by the EPC program. This approach incorporates five key domains: study limitations, consistency, directness, precision, and reporting bias.

We determined study limitations by appraising the degree to which the included studies for a given outcome had adequate protection against bias (i.e., have good internal validity). If the evidence permits a conclusion, then, all else being equal, a set of studies at low risk of bias yields a higher SOE rating than a set of studies at high risk of bias.

We assessed consistency of results for the same outcome among the available studies in terms of the direction and magnitude of effect. We downgraded for inconsistency when there was heterogeneity in the effects of an intervention across studies when measured by the same

outcome that could not be explained through identifiable differences in study characteristics. We downgraded for unknown consistency when only a single study was included for an outcome.

The evidence was considered indirect if the populations, interventions, comparisons, or outcomes used within studies did not directly correspond to the comparisons we were evaluating.

Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome and may be affected by sample size, number of events, and width of confidence intervals. We also considered the evidence to be imprecise when key components of the outcome data provided by studies were not fully reported (e.g., measures of variance were not included), or when it was not possible to derive an estimate of effect based on the available data. In some cases, we downgraded the strength of evidence by two levels due to substantial imprecision resulting from very small samples or numbers of events.

Reporting bias includes publication bias, outcome-reporting bias, and analysis reporting bias. Given the small number of studies we evaluated for most of the interventions (and the lack of effect for interventions that were more widely studied); we did not examine funnel plots. We downgraded for reporting bias when we detected a likelihood of outcome reporting bias (important clinical outcomes appear to have been collected but not reported by the studies within a comparison) or analysis reporting bias (important comparisons were not analyzed). For studies pertaining to KQ 1 that had commercial funding and/or authorship, we also assessed the size and direction of any effect in comparison to the studies that did not receive commercial support, to identify possible publication or reporting bias.

Applicability

Several *a priori* factors may limit the applicability of findings. Many studies included children under age 11, youths age 12 and up, and adults, making it difficult to apply the findings to a single age group. Studies also often focused on patients at high risk for exposure to allergens, and this may not represent the general asthma population. Another important consideration is that many patients with asthma in the "real world" may be renters rather than homeowners or may have limited financial means and, therefore, may have limited opportunity to implement certain types of interventions, such as carpet removal.

Results

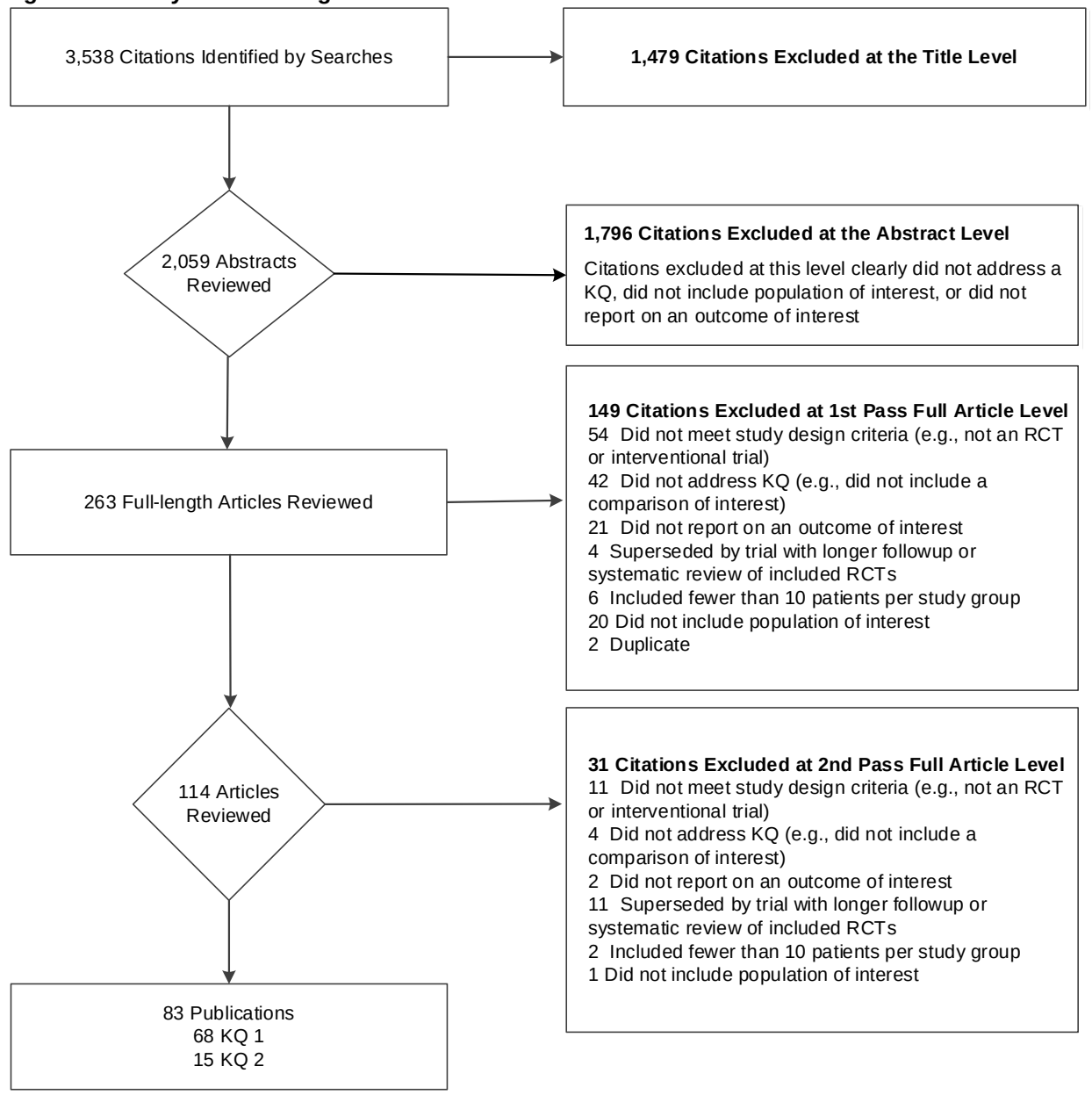
Introduction

We begin by describing the results of our literature searches. We then provide a brief description of the included studies. The remainder of the chapter is organized by Key Question (KQ). For each KQ, we provide a detailed description of the studies, key summary points, a detailed analysis of the results, and tables that present the strength of evidence (SOE).

Results of Literature Searches

The literature searches identified 83 articles (see Figure 2). Sixty-eight publications (including 57 RCTs with data published in 61 articles) addressed KQ 1, and 15 studies (including 3 RCTs) examined KQ 2. Articles that were excluded at the full-text level with reasons for their exclusion are listed in Appendix B.

Figure 2. Study attrition diagram



KQ=key question; RCT-randomized controlled trial

Key Question 1. Among individuals with asthma, what is the effectiveness of interventions to reduce or remove exposure to indoor inhalant allergens on asthma control, exacerbations, quality of life, and other relevant outcomes?

Description of Included Studies

Our searches identified studies that addressed the following specific interventions:

- Acaricide (i.e., house dust mite pesticide applied to carpets, mattresses, and/or furniture)
- Air purification (i.e., devices designed to filter room air)
- Carpet removal (i.e., removal of carpeting or area rugs type from one or more rooms)
- High-energy particulate air-filtration (HEPA) vacuum (i.e., routine use of HEPA vacuum for cleaning carpeting or rugs of any type)
- Mattress covers (i.e., impermeable covers placed on mattresses) and laundering of linens
- Mold removal (i.e., professional cleaning of mold covered surfaces)
- Pest control (i.e., traps, poison, and/or professional services designed to control common house pests such as cockroaches and mice)
- Pet removal (i.e., confinement to specific rooms within a house, or complete removal of furry pets such as dogs and cats)
- Multicomponent interventions with more than one strategy for reducing one or more allergen exposures

For clarity, individual study information and SOE for the different interventions are reported in separate tables. Fifty-seven RCTs and seven nonrandomized or pre-post trials addressed this KQ. Due to the heterogeneity of the included studies, we did not attempt to combine data from the studies quantitatively. Instead, we provide a narrative synthesis. Detailed evidence tables presenting information on the design of the studies, study populations, findings, and assessment of study limitations (risk of bias) are located in Appendix C. In accordance with the approach used by Guidelines for the Diagnosis and Management of Asthma (EPR-3) sponsored NAEPP, we have defined "pediatric" or "child" populations as including patients age 11 or younger, and "adult" populations as including youths age 12 or older and adults.[1] Studies that include patients in both categories are described as having a "mixed population."

Table 2, below, provides an overview of the distribution of the studies addressing KQ 1.

Table 2. Overview of interventional studies for reducing exposure to allergens

Intervention	Randomized Controlled Trials and Sample Size	Other Study Designs and Sample Size	Age Cohorts by Study Design*	Country/Region
Acaricides (dust mite pesticide)	6 Total n=227 (Range 26–62)	1 nonrandomized trial n=59	2 adult 1 pediatric 4 mixed	6 Europe 1 Canada
Air purification	9 n=311 (Range 10–119)	0	3 adult 1 pediatric 5 mixed	1 United States 7 Europe 1 New Zealand
Carpet removal	0	0	Not applicable	Not applicable
HEPA vacuums	1 n=60	0	1 mixed	1 Europe

Table 2. Overview of interventional studies for reducing exposure to allergens (continued)

Intervention	Randomized Controlled Trials and Sample Size	Other Study Designs and Sample Size	Age Cohorts by Study Design*	Country/Region
Mattress covers	16 n=2,003 (Range 20–1,122)	0	9 adult 1 pediatric 5 mixed 1 not reported	10 Europe 4 Asia 2 Australia
Mold removal	0	0	Not applicable	Not applicable
Pest control	0	1 pre-post n=78	1 pediatric	1 United States
Pet removal	0	0	Not applicable	Not applicable
Other (1 study of bleach cleaning)	1 n=97	0	1 mixed	1 United States
Multicomponent	24 n=3,977 (Range 23–937)	3 pre-post (n=365) 2 nonrandomized controlled trials (n=204)	5 adult 7 pediatric 17 mixed	19 United States 9 Europe 1 Australia
Total	57	3 nonrandomized trials 4 pre-post	19 adult 11 pediatric 33 mixed 1 not reported	22 United States 1 Canada 33 Europe 4 Asia 4 Australia

* Adult=all patients were ≥12 years old; HEPA: high-energy particulate air-filtration; Mixed=study included pediatric and adult patients; Pediatric=all patients were <12 years old;

Key Points

- Fifty-seven RCTs and seven nonrandomized or pre-post trials addressed this KQ.
- Twenty-eight of the studies assessed individual interventions and twenty-nine of the studies assessed multicomponent interventions.
- Studies infrequently reported validated measures of asthma control, limiting our ability to fully evaluate the efficacy of the interventions.
- Acaricide (dust mite pesticide) use was not associated with changes in pulmonary function when assessed as an individual intervention (SOE: Low) or as part of a multicomponent strategy (SOE: Moderate). Effects on other asthma outcomes were inconclusive for both individual and multicomponent studies that included acaricide.
- Air purification devices, evaluated as a lone intervention, did not affect healthcare utilization (SOE: Low) but did improve quality of life (SOE: Low). When included as part of a broader multicomponent approach, air purification had no effect on exacerbations (SOE: Moderate) or quality of life (SOE: Moderate), but was associated with reduced school absenteeism (SOE: Low). Insufficient evidence exists to draw any conclusions regarding the effect of these devices on other outcomes.
- Carpet removal was not examined as an individual intervention, but was addressed in eight of the multicomponent studies. The evidence is insufficient to support any conclusions regarding asthma control or other outcomes.
- High-energy particulate air-filtration (HEPA) vacuums were evaluated in only one single-intervention study, with inconclusive results. In eight multicomponent studies, HEPA vacuums were associated with fewer exacerbations (SOE: Moderate) and improved quality of life (SOE: Moderate) in pediatric patients, but these benefits were not observed in studies that included both adults and children.
- Impermeable mattress covers were the most commonly examined intervention. Use of these covers alone was associated with no effect on exacerbations, use of rescue

medications, or quality of life (SOE: High). When incorporated into multicomponent strategies, mattress covers were associated with fewer missed days of school or activities (SOE: Low), but no effect on emergency department visits (SOE: Low), hospitalizations (SOE: High), or quality of life (SOE: Moderate).

- Mold removal was not examined as an individual intervention, but was addressed in five multicomponent studies. The evidence was inconclusive.
- One study of pest control as a single intervention yielded inconclusive evidence. Pest control strategies were included in 12 multicomponent studies, and were associated with fewer exacerbations (SOE: Moderate), reduced school absenteeism (SOE: Low), and improved quality of life (SOE: Low), but there was no effect on acute care clinic visits (SOE: High) or worker absenteeism (SOE: Low). The evidence for other outcomes was inconclusive.
- No studies were identified that focused solely on pet removal to improve asthma control. Two studies examining multicomponent interventions included pet removal in addition to other strategies, but this component could not be evaluated because pet removal was not uniformly implemented, and stratified results were not reported.

Detailed Synthesis

Studies of Individual Interventions

Individual interventions for which we identified studies include treatment of mattresses and carpets with acaricide, use of air purifiers, HEPA vacuuming, mattress covers, and pest control. We also found one study of a commercially available cleaning product. Adverse events from the interventions listed below were not expected and none were reported. While many studies reported on pulmonary physiology, non-validated measures of respiratory symptoms, and allergen levels, few studies reported validated measures of asthma control or quality of life. Additionally, rates of exacerbations and healthcare utilization were often low or not reported.

Acaricide (Dust Mite Pesticide)

Five RCTs[21-25] and one non-RCT[26] compared the use of acaricide to placebo. Two RCTs[21,27] and the non-RCT[26] compared the use of acaricide to other HDM avoidance interventions. Treatments were used on carpets, upholstery, and mattresses in the bedroom and typically applied in the most commonly used residential room. Followup ranged from 3 to 6 months. The trials reported that all enrolled patients demonstrated allergic sensitization to HDM allergen. Acaricide manufacturers funded two studies but they did not report positive findings and we did not detect publication or reporting bias in this evidence base. Measures of asthma control, exacerbations, and healthcare utilization were not reported in the studies. Use of acaricide in the home was associated with no change in pulmonary physiology (SOE: Low). The findings for quality of life were inconclusive, and interpretation of the findings was limited by poor reporting of data and statistical analyses, and small sample sizes. Table 3 below presents the findings and SOE ratings for the outcomes these studies assessed.

Table 3. Strength of evidence for acaricide (dust mite pesticide) interventions

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
Acaricide vs. placebo	Asthma control	**Not evaluable:** Not reported in included studies.	NA	NA
	Exacerbations	**Not evaluable:** Not reported in included studies.	NA	NA
	Healthcare utilization	**Not evaluable:** Not reported in included studies.	NA	NA
	Pulmonary physiology: spirometry	**No effect:** No reported differences between acaricide and placebo for spirometry measures.	4 RCTs[21-24] 1 non-RCT[26] n=168	Low (Study limitations, Imprecise)
	Pulmonary physiology: airway hyper-responsiveness	**Inconclusive:** RCT found no difference between acaricide and placebo, and non-RCT reported a statistically significant but not clinically significant improvement in PC_{20} following use of acaricide.	1 RCT[23] 1 non-RCT[26] n=66	Insufficient (Study limitations, Inconsistent, Imprecise)
	Quality of Life	**Inconclusive:** Small RCT showed no between-group difference in quality of life; data shown graphically with no estimation of variability.	1 RCT[21] n=30	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Symptoms (secondary measure)	**Inconclusive:** Small RCT found improvements in both parent and physician evaluation of asthma severity, but no differences in frequency of wheezing.	1 RCT[25] n=35	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Allergen levels: Environmental measures (secondary measure)	**Inconclusive:** Small RCT[25] showed decreased levels of Der f in both groups, with a greater decrease in the acaricide group. Another small RCT[22] showed no difference between groups for Der f and Der p allergens in carpet or mattress, but found a reduction of HDM allergens in "other" areas of the house. The remaining studies found no differences between treatment groups.	4 RCTs[21,22,24,25] 1 non-RCT[26] n=177	Insufficient (Study limitations, Inconsistent, Imprecise)
Acaricide vs. other mite-avoidance interventions	Asthma control	**Not evaluable:** Not reported in included studies.	NA	NA
	Exacerbations	**Not evaluable:** Not reported in included studies.	NA	NA
	Healthcare utilization	**Not evaluable:** Not reported in included studies.	NA	NA
	Pulmonary physiology	**No effect:** No reported differences between acaricide and other mite-avoidance interventions for spirometry measures.	2 RCTs[21,27] 1 non-RCT[26] n=95	Low (Study limitations, Imprecise)
	Quality of life	**Inconclusive:** 1 small RCT showed no between-groups difference in quality of life; test statistics not reported.	1 RCT[27] n=26	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Symptoms (secondary measure)	**Not evaluable:** Not reported in included studies.	NA	NA
	Allergen levels (secondary measure)	**Inconclusive:** No studies showed between-group differences in allergen levels, but data were not reported in a manner that allowed assessment of precision.	2 RCTs[21,27] 1 non-RCT[26] n=95	Insufficient (Study limitations, Imprecise)

[a]Outcomes of Asthma control, Exacerbations, Healthcare utilization, and Pulmonary physiology as defined by Asthma Outcomes workshop;[28] outcomes of Quality of life, Symptoms, and Allergen levels as defined by study authors.
[b]Study limitations derived from Risk of Bias assessments in Appendix C.
Der p=*dermatophagoides pteronyssinus* allergen; HDM=house dust mite; IgE=immunoglobulin E; NA=not available; RCT=randomized controlled trial air purification interventions

Three of nine RCTs compared the use of air filtration or air purifiers to either a sham intervention[29,30] or no intervention.[31] One RCT[32] compared the use of air filtration to other HDM-avoidance interventions. One study installed new mechanical heat-recovery ventilation in the home, with sham fans as a control.[29] The remaining four studies used air filtration or air purifiers in the bedroom, and most also placed air purifiers in the living room. Followup ranged from 4 weeks to 12 months. Three of the nine studies reported that all patients were sensitized to at least one allergen of interest that was potentially subject to the effects of the intervention, usually HDM, cat, or dog. Three other studies found that a majority of patients were sensitized to one of these allergens, while the other three reported that a minority of patients had positive allergy tests to any given allergen. Air filtration device manufacturers funded three studies, but we did not detect publication or reporting bias in this evidence base because the industry-funded studies were not associated with better results than non-industry funded studies of air purifiers. The findings for asthma control and pulmonary physiology were inconclusive, and healthcare utilization was not reported. There was no difference in exacerbations (SOE: Low). For quality of life, one study found that AQLQ scores improved (SOE: Low), while two studies that used non-validated quality of life measures found no effect (SOE: Low). Interpretation of all the findings reported for this intervention was limited by poor reporting of data and statistical analyses, lack of between-group comparisons, and small sample sizes. Table 4 below presents the findings and SOE ratings for the outcomes these studies assessed.

Table 4. Strength of evidence for air purification interventions

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
Air filtration/air purifier vs. control	Asthma control	**Inconclusive:** 1 RCT with low risk of bias showed no differences in ACQ scores. 1 RCT with high risk of bias showed an improvement in combined asthma outcomes following use of air cleaners. 1 RCT[30] did not report differences in asthma scores between interventions.	3 RCTs[29-31] n=169	Insufficient (Study limitations, Inconsistent, Imprecise)
	Exacerbations	**Not evaluable:** Not reported in included studies.	NA	NA
	Healthcare utilization	**No effect:** Measures of ED visits and use of rescue medications did not differ between treatment conditions.	2 RCTs[29,33] n=242	Low (Study limitations, Imprecise)
	Pulmonary physiology	**Inconclusive:** 1 RCT[29] showed improvements in evening peak flow, but in no other spirometry measures. 1 RCT[34] showed improvements in peak flow variation and airway hyper-responsiveness but not in FEV_1. 5 other RCTs showed no differences in spirometry measures.	7 RCTs[29-31,33-36] n=281	Insufficient (Study limitations, Inconsistent, Imprecise)
	Quality of life: mini-AQLQ	**Improvement:** 1 RCT[33] found significant improvement in mini-AQLQ scores for active air cleaners compared to placebo (mean difference in change [SEM], active – placebo = 0.54 (0.28); p<0.05).	1 RCT[33] n=183	Low (Study limitations, Unknown consistency)
	Quality of life: other measures	**No effect:** 2 RCTs showed no between-group differences in quality of life.	2 RCTs[29,35]	Low (Study limitations, Imprecise)
	Symptoms (secondary measure)	**Inconclusive:** Following intervention, 1 RCT[37] reported improvements in asthma symptoms but provided no summary statistics.	1 RCT[37]	Insufficient (Study limitations, Inconsistent, Imprecise)

Table 4. Strength of evidence for air purification interventions (continued)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
	Allergen levels (secondary measure)	**Inconclusive:** 1 small RCT[30] showed decreased levels of Der p during the active intervention compared to placebo. 4 RCTs[29,31,34,35] found no differences between treatment groups. Finally, 3 RCTs did not report allergen levels.[33,36,37]	8 RCTs[29-31,33-37] n=281	Insufficient (Study limitations, Inconsistent, Imprecise)
Air filtration/air purifier vs. other mite avoidance interventions	Asthma control	**Not evaluable:** Not reported in included studies.	NA	NA
	Exacerbations	**Not evaluable:** Not reported in included studies.	NA	NA
	Healthcare utilization	**Not evaluable:** Not reported in included studies.	NA	NA
	Pulmonary physiology	**Inconclusive:** 1 RCT showed no differences for FEV_1, vital capacity, or airway hyper-responsiveness. Data were shown graphically with no estimate of variability; analyses for between-group comparisons not reported.	1 RCT[32] n=30	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Quality of life	**Not evaluable:** Not reported in included studies.	NA	NA
	Symptoms (secondary measure)	**Not evaluable:** Not reported in included studies.	NA	NA
	Allergen levels (secondary measure)	**Inconclusive:** Between-groups analyses not reported.	1 RCT[32] n=30	Insufficient (Study limitations, Unknown consistency, Imprecise)

[a]Outcomes of Asthma control, Exacerbations, Healthcare utilization, and Pulmonary physiology as defined by Asthma Outcomes workshop;[28] outcomes of Quality of life, Symptoms, and Allergen levels as defined by study authors.
[b]Study limitations derived from Risk of Bias assessments in Appendix C.
ACQ=asthma control questionnaire; AQLQ=asthma quality of life questionnaire; Der p=*dermatophagoides pteronyssinus* allergen; ED=emergency department; FEV_1=forced expiratory volume in 1 second; HDM=house dust mite; NA=not available; RCT=randomized controlled trial; SEM=standard error of the mean

Carpet Removal

We did not identify any studies that examined carpet removal as a solitary intervention to improve asthma outcomes. Carpet removal was included as a strategy in several multicomponent interventions that are described in the multicomponent study section below.

HEPA Vacuum Interventions

One small RCT[38] compared the use of HEPA vacuums on carpets and soft furnishings to standard vacuums. Participants were instructed to vacuum the sofa, mattress, and living room and bedroom carpet at least once a week for up to one year. All patients were sensitized to HDM, and a majority of those who owned a cat were also allergic to cat allergen. This study was not funded by an industry source, although one coauthor reported having received funding from a vacuum manufacturer. Measures of asthma control, exacerbations, healthcare utilization, or quality of life were not reported. Use of HEPA vacuums led to improvements in spirometry measures compared to the standard vacuums, but the overall SOE was Insufficient. Use of HEPA vacuums reduced the secondary measure of allergen levels compared to baseline for some areas of the home, and some of the allergens measured, but most areas and allergens did not vary with

use of the HEPA vacuum. In addition, between-group comparisons were not reported, limiting interpretation of the findings. Table 5 below presents the findings and SOE ratings for the outcomes this study assessed.

Table 5. Strength of evidence for HEPA vacuum interventions

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
HEPA vacuum vs. standard vacuum	Asthma control	**Not evaluable:** Not reported in included studies.	NA	NA
	Exacerbations	**Not evaluable:** Not reported in included studies.	NA	NA
	Healthcare utilization	**Not evaluable:** Not reported in included studies.	NA	NA
	Pulmonary physiology	**Inconclusive:** 1 RCT showed improvements in FEV_1 and peak flow, but only p-values were reported for between-group comparisons.	1 RCT[38] n=60	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Quality of life	**Not evaluable:** Not reported in included studies.	NA	NA
	Symptoms (secondary measure)	**Not evaluable:** Not reported in included studies.	NA	NA
	Allergen levels (secondary measure)	**Inconclusive:** Between-group comparisons not reported. Use of HEPA vacuum reduced allergen levels compared to baseline for some areas and allergens.	1 RCT[38] n=60	Insufficient (Study limitations, Unknown consistency, Imprecise)

*Outcomes of Asthma control, Exacerbations, Healthcare utilization, and Pulmonary physiology as defined by Asthma Outcomes workshop;[28] outcomes of Quality of life, Symptoms, and Allergen levels as defined by study authors.
[b]Study limitations derived from Risk of Bias assessments in Appendix C.
FEV_1=forced expiratory volume in 1 second; HEPA=high efficiency particulate air; NA=not available; RCT=randomized controlled trial

Mattress Cover Interventions

Sixteen RCTs examined the effectiveness of mattress covers or other interventions related to bedding. Nine of these RCTs[39-47] compared the use of impermeable mattress covers to placebo, and four other RCTs[48-51] compared covers to no intervention. We combined these 13 studies for analysis. An additional three RCTs evaluated different interventions: one[52] studied feather-filled pillows and quilts, with impermeable mattress covers used in both the intervention and control groups; one[53] compared an impermeable pillow designed to resist HDM without any additional covering, to a placebo pillow; and one[54] examined the effectiveness of boiling bed covers in hot water for 10 minutes and exposing them to sunlight for 3 hours every 2 weeks, compared with standard linen washing practices. None of the studies was conducted in the United States, and most were small; nine studies included fewer than 50 patients, and only four studies included more than 100 patients. Ten studies included only patients age 12 or older, five included both adults and youths below age 12, and the study of the impermeable pillow enrolled only children. One study did not report the ages of enrolled participants. Fifteen of the 16 studies confirmed that all patients demonstrated sensitization to HDM allergens. Only six studies described randomization and allocation practices, but 10 studies blinded both patients and outcome assessors. No studies reported direct funding by mattress cover manufacturers, although one study included two coauthors who had received funding from a manufacturer. Individual study risk of bias was not considered a limitation of the evidence base addressing mattress covers.

Asthma control measures were not reported in these studies. No effect was observed for exacerbations (SOE: High), use of inhaled corticosteroids (SOE: Low), use of rescue medication (SOE: High), pulmonary physiology (SOE: High), or quality of life (SOE: High). However, the evidence suggests that secondary measures of HDM allergen levels were significantly reduced by use of mattress covers (SOE: Moderate) despite the lack of clinical improvement. Findings for the three studies that did not evaluate mattress covers were inconclusive. Table 6 below presents the findings and SOE ratings for the outcomes these studies assessed.

Table 6. Strength of evidence for mattress cover interventions

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
Impermeable covers on mattress, pillow, and/or duvet vs. placebo covers or no intervention	Asthma control	**Not evaluable:** Not reported in included studies.	NA	NA
	Exacerbations	**No effect:** No difference in composite measure of hospitalization and/or rescue medication use in RCT of 1,122 adults. No difference in frequency of asthma attacks in RCT of 55 adults.	2 RCTs[43,44] n=1,177	High
	Healthcare utilization: inhaled corticosteroid use	**No effect:** No difference for total dosage change in RCT of 126 adults. No difference for mean change in 28-day dose in RCT of 47 mixed-population subjects. Significantly greater reduction in mean daily dose in RCT of 60 mixed population.	3 RCTs[39,42,46] n=233	Low (Inconsistent, Imprecise)
	Healthcare utilization: rescue medication use	**No effect:** No difference in 2 RCTs of 1,154 adults and 2 RCTs of 91 mixed- population subjects for beta agonist use or dose. No difference in use of undefined "rescue medication" in RCT of 30 adults.	5 RCTs[40,42,44,45,47] n=1,275	High
	Healthcare utilization and costs: work absenteeism	**Decreased workdays:** Significant decrease in missed days of work in RCT of 1,122 adults, but difference may not be meaningful: Mean difference: -0.15 days per month (95% CI: -0.29 to -0.02).	1 RCT[44] n=1,122	Low (Unknown consistency, Imprecise)
	Pulmonary physiology	**No effect:** No difference in morning or evening peak flow for 8 RCTs of 1,535 adults and 4 RCTs of 158 mixed- population subjects. Significant improvement reported in RCT of 25 adults.	13 RCTs[39-51] n=1,719	High
	Quality of life	**No effect:** No difference in 5 RCTs of 1,365 adults; 2 used the Modified AQLQ-Marks; 1 used mini-AQLQ; 1 used St George's Respiratory Questionnaire; 1 used Quality of Life for Respiratory Illness Questionnaire	5 RCTs[39,40,43-45] n=1,365	High
	Symptoms (secondary measure)	**No effect:** No difference in 7 RCTs (n=1,470; 4 in adults and 3 in mixed populations.) Significant improvement in RCT of 25 adults, Studies used similar but not identical sets of composite scores, ranging from 3 to 8 discrete items (e.g., cough, wheeze)	8 RCTs[39,40,42,44-48] n=1,495	High
	Allergen levels (secondary measure)	**Allergen reduction:** Significant reduction in Der p and/or Der f allergen in 6 RCTs of 1,387 adults and 2 RCTs of 91 mixed population subjects. No difference in 2 RCTs of 141 adults.	10 RCTs[39-45,47,48,51] n=1,619	Moderate (Imprecise)
Feather-filled pillow and quilt	Asthma control	**Not evaluable:** Not reported in included studies.	NA	NA

Table 6. Strength of evidence for mattress cover interventions (continued)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
vs. impermeable cover on mattress, pillow, and quilt	Exacerbations	**Not evaluable:** Not reported in included studies.	NA	NA
	Healthcare utilization	**Not evaluable:** Not reported in included studies.	NA	NA
	Pulmonary physiology	**Not evaluable:** Not reported in included studies.	NA	NA
	Quality of life	**Inconclusive:** No difference for overall quality of life: Adjusted difference effect: 0.04 (95% CI: -0.27 to 0.35; p=0.80).	1 RCT[52] n=197	Insufficient (Unknown consistency, Imprecise)
	Symptoms (secondary measure)	**Inconclusive:** No difference for frequent wheeze, speech-limiting wheeze, or sleep disturbance caused by wheeze.	1 RCT[52] n=197	Insufficient (Unknown consistency, Imprecise)
	Allergen levels (secondary measure)	**Inconclusive:** No difference for Der p 1 allergen: Median exposure: 16.0 pg-m3 (IQR: 1.0 to 54.1) vs. 28.0 pg-m3 (IQR: 1.0 to 66.8, p=0.30).	1 RCT[52] n=197	Insufficient (Unknown consistency, Imprecise)
Impermeable pillow vs. placebo pillow	Asthma control	**Not evaluable:** Not reported in included studies.	NA	NA
	Exacerbations	**Inconclusive**: No difference in number of asthma attacks (data reported in graph and cannot be evaluated.)	1 RCT[53] n=20	Insufficient (Unknown consistency, Imprecise, Reporting Bias Detected)
	Healthcare utilization	**Not evaluable:** Not reported in included studies.	NA	NA
	Pulmonary physiology	**Not evaluable:** Not reported in included studies.	NA	NA
	Quality of life	**Not evaluable:** Not reported in included studies.	NA	NA
	Symptoms (secondary measure)	**Not evaluable:** Not reported in included studies.	NA	NA
	Allergen levels (secondary measure)	**Inconclusive:** No difference in IgE levels for HDM (data reported in graph and cannot be evaluated.)	1 RCT[53] n=20	Insufficient (Unknown consistency, Imprecise, Reporting Bias Detected)
Cotton bed covers boiled and exposed to 3 hours of sunlight every 2 weeks vs. standard laundering	Asthma control	**Not evaluable:** Not reported in included studies.	NA	NA
	Exacerbations	**Inconclusive:** No difference in asthma attacks.	1 RCT[54] n=42	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Healthcare utilization	**Not evaluable:** Not reported in included studies.	NA	NA
	Pulmonary physiology	**Inconclusive:** No difference for morning or evening peak flow.	1 RCT[54] n=42	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Quality of life	**Not evaluable:** Not reported in included studies.	NA	NA

Table 6. Strength of evidence for mattress cover interventions (continued)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
	Symptoms (secondary measure)	**Inconclusive:** No difference for frequency of cough, wheeze, or sputum. Significant reduction in frequency of dyspnea.	1 RCT[54] n=42	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Allergen levels (secondary measure)	**Inconclusive:** No difference between groups.	1 RCT[54] n=42	Insufficient (Study limitations, Unknown consistency, Imprecise)

*Outcomes of Asthma control, Exacerbations, Healthcare utilization, and Pulmonary physiology as defined by Asthma Outcomes workshop;[28] outcomes of Quality of life, Symptoms, and Allergen levels as defined by study authors.
[b]Study limitations derived from Risk of Bias assessments in Appendix C.
CI=confidence interval; Der f=*dermatophagoides farina* allergen; Der p=*dermatophagoides pteronyssinus* allergen; HDM=house dust mite; IgE=immunoglobulin E; IQR=interquartile range; NA=not available; pg-m3=phosphoglucomutase 3 gene; RCT=randomized controlled trial

Mold Removal

We did not identify any studies that examined mold removal as a solitary intervention to improve asthma outcomes. Mold removal was included as a strategy in several multicomponent interventions that are described in the multicomponent study section below.

Pest Control Interventions

One nonrandomized pre-post study[55] examined a multicomponent pest-reduction intervention targeted primarily at cockroach and rodent elimination. The intervention was conducted in public housing in Boston, MA, and consisted of a one-time deep-cleaning of the home, setting traps, sealing rodent access points, replacement of mattresses, education about kitchen hygiene and food storage, reducing clutter, and communications with housing authority and pest contractors. Followup times varied, with a maximum followup of 66 weeks. Sixty percent of patients were sensitized to HDM allergens, while 58 percent reported sensitization to cockroach allergen. Measures of asthma control, healthcare utilization, pulmonary physiology, and quality of life were not reported, and the evidence for exacerbations was inconclusive. Over time, secondary measures of respiratory symptoms improved and allergen levels were reduced compared to baseline. Lack of precision in reporting the findings and small sample size limit the ability to draw conclusions regarding effectiveness of the interventions. Table 7 below presents the findings and SOE ratings for the outcomes this study assessed.

Table 7. Strength of evidence for pest control interventions

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
Pest reduction interventions pre- and post-treatment	Asthma control	**Not evaluable:** Not reported in included studies.	NA	NA
	Exacerbations	**Inconclusive**: Pre-post study found no change in rates of exacerbations. Overall rates described as low (data not reported).	1 pre-post study[55] n=78	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Healthcare utilization	**Not evaluable:** Not reported in included studies.	NA	NA
	Pulmonary physiology	**Not evaluable:** Not reported in included studies.	1 pre-post study[55] n=78	NA
	Quality of life	**Not evaluable:** Not reported in included studies.	NA	NA
	Symptoms (secondary measure)	**Inconclusive:** Significant improvement in respiratory symptoms. No estimation of variability reported.	NA	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Allergen levels (secondary measure)	**Inconclusive:** All allergens were reported to be decreased from baseline, with no statistical analysis or description of statistical significance reported.	1 pre-post study[55] n=78	Insufficient (Study limitations, Unknown consistency, Imprecise)

*Outcomes of Asthma control, Exacerbations, Healthcare utilization, and Pulmonary physiology as defined by Asthma Outcomes workshop;[28] outcomes of Quality of life, Symptoms, and Allergen levels as defined by study authors.
[b]Study limitations derived from Risk of Bias assessments in Appendix C.
NA=not available

Pet Care and Removal

We did not identify any studies that examined pet care or pet removal as a solitary intervention to improve asthma outcomes. Pet removal was included as a strategy in two multicomponent interventions that are described below.

Other Interventions

One RCT[56] compared the use of cleaning products to no cleaning products. Many of the cleaning products contained dilute 0.09% sodium hypochlorite, and all but three were commercially available, but the data for outcomes related to asthma control were not stratified by type of cleaning product. A manufacturer of cleaning products funded the study, and the authors did not report how many patients were sensitized to specific allergens. In this 8-week study, measures of asthma control and exacerbations were inconclusive. Healthcare utilization and pulmonary physiology outcomes were not reported. Furthermore, the main outcome of quality of life was improved in all groups, including the no-cleaning-product group, and the authors suggest the possibility of a placebo effect of keeping diaries on quality of life. Secondary asthma symptom outcomes were improved with use of any experimentally provided cleaner compared to no cleaning product. However, allergen levels in dust samples were not affected. Table 8 below presents the findings and SOE ratings for the outcomes this study assessed.

Table 8. Strength of evidence for other interventions

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
Cleaning products vs. no cleaning products	Asthma control	**Inconclusive:** Not possible to determine effectiveness of hypothesized effective intervention of sodium hypochlorite.	1 RCT[56] 97 families	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Exacerbations	**Inconclusive:** Overall rates of exacerbations described as low for all groups (data not shown).	1 RCT[56] 97 families	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Healthcare utilization	**Not evaluable:** Not reported in included studies.	NA	NA
	Pulmonary physiology	**Not evaluable:** Not reported in included studies.	NA	NA
	Quality of Life	**Inconclusive:** Main outcome of quality of life was improved in all groups; authors note possibility of placebo effect due to keeping diaries in-group with no cleaning products.	1 RCT[56] 97 families	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Symptoms (secondary measure)	**Not evaluable:** Not reported in included studies.	NA	NA
	Allergen levels (secondary measure)	**Inconclusive:** Levels of all dust allergens did not vary statistically as a function of treatment group. Comparative data of allergens not shown for cleaning vs. no cleaning in asthma participants.	1 RCT[56] 97 families	Insufficient (Study limitations, Unknown consistency, Imprecise)

*Outcomes of Asthma control, Exacerbations, Healthcare utilization, and Pulmonary physiology as defined by Asthma Outcomes workshop;[28] outcomes of Quality of life, Symptoms, and Allergen levels as defined by study authors.
[b]Study limitations derived from Risk of Bias assessments in Appendix C.
NA=not available; RCT=randomized controlled trial

Studies of Multicomponent Interventions

Twenty-four RCTs,[57-80] two nonrandomized trials with concurrent controls,[81,82] and three pre-post studies[83-85] examined interventions that bundled multiple allergen-avoidance strategies. Six of the 29 studies included application of an acaricide to carpeting. Three studies used air filtration devices. Eight studies recommended or required removal of carpeting in living rooms, bedrooms, or both. Eight studies provided participants with HEPA-filtered vacuums. Eighteen studies included use of impermeable mattress covers. An intervention intended to reduce or remove mold was included in five studies. Twelve studies implemented pest control strategies. Pet removal was incorporated as a suggestion to reduce pet-related allergens within two studies. In 11 studies, patients were provided general cleaning supplies, to help minimize allergens, dust, dirt, and other irritants. Additionally, 14 studies featured a community health worker, social worker, or study team member who visited patient homes to provide direct, tailored education about management of the home environment and offer instruction in the proper use of intervention tools such as mattress covers or vacuums. Finally, 16 studies included some other type of intervention as well, addressing a wide range of potential strategies.

Nineteen of the 29 studies were conducted in the United States. Seven studies were conducted exclusively in children, five studies enrolled adults and youths age 12 and up, and the

remaining 17 studies included all populations. Most of the studies have important limitations that increase potential risk of bias: only six of 24 RCTs described an acceptable randomization protocol, just three described a procedure for allocation concealment, and nine included blinding of both patients and outcome assessors. Attrition was also a substantial barrier, with 12 RCTs reporting attrition rates exceeding 15 percent. Only one study reported funding from a commercial source that manufactured the intervention that was studied. Risk of bias from selective outcome reporting was judged to be low in 19 studies, and risk of bias from incomplete data reporting was judged to be low in about half of the studies. Detailed information on risk of bias for all studies is found in Appendix C.

Another important factor is whether sensitization to the relevant allergen (targeted by the intervention) was assessed in participants prior to the intervention. Of the 24 RCTs, 10 reported that all enrolled patients were allergic to at least one allergen of interest (usually HDM), proven most often by a positive skin prick test. Seven other RCTs reported that a majority of patients were sensitized, while four reported smaller rates. Three studies did not report sensitization in the study participants.

Given the substantial heterogeneity in the combination of interventions used in these multicomponent studies, as well as variability in implementation and adherence to the interventions, we organized the SOE analysis according to the concept of "grouping by active component."[86] In this approach, each active component was examined by synthesizing the studies that shared a common element in the intervention arm (e.g., use of acaricide), without regard to the other active intervention components in those studies. The "active" components are interventions that were present in the intervention arm but not the control arm of each study, and are within the scope of this review. These active components correlate with the single intervention studies described above: acaricide, air purification, carpet removal, HEPA vacuums, mattress covers, mold removal, pest control, and pet removal. A study that had three different active interventions (e.g., HEPA vacuum, mattress cover, pest control) would therefore be included in the SOE table three different times as it was combined with other studies that shared each respective active intervention. Although this approach limits our confidence in the results by temporarily attributing the outcomes of a complex study to only one of its components in each analysis, we believe this is the best approach to synthesize this evidence in the context of a highly heterogeneous evidence base. We considered two alternative analytic approaches as well. First, we attempted to group the studies into "bundles" that could be characterized by a set of shared components. This was not feasible, however, because the specific combinations of interventions were too diverse, and this approach would have yielded many sets of bundles with minimal numbers of studies in each set. A second approach was to compare studies that had positive findings (i.e., improvement in the primary clinical outcomes) to studies that found no effect, and identify differences in the types of interventions used. This analysis did not detect a pattern of intervention components that was more likely to be present in positive studies.

Some of the interventions that appear frequently in the studies are excluded from this analysis because they are outside the scope of the review (e.g., community health workers providing education beyond information on allergen reduction strategies.) Additionally, pet removal was not assessed because it was a component of only two studies and within those studies, pet ownership was not an inclusion criterion (i.e., any participants who had pets were encouraged to remove them or restrict their access, but the intervention was not standardized). Table 9 presents an overview of the interventions by study.

Table 9. Multicomponent indoor allergen reduction interventions by study

Study	Acaricide (dust mite pesticide)	Air Purification	Carpet Removal[a]	HEPA Vacuum	Mattress Covers	Mold Removal	Pest Control	Pet Removal[a]	Laundering Linens	Cleaning Supplies Provided	CHW Education/ Instruction	Other
DiMango et al. 2016[57]		✓		✓	✓					✓		
Shani et al. 2015[83]*					✓		✓			✓	✓	
Breysse et al. 2014[81]*			✓			✓						Weatherization
Turcotte et al. 2014[84]*				✓			✓			✓	✓	Professional cleaning
Sweet et al. 2013[85]*				✓	✓	✓	✓			✓	✓	Moisture control
El-Ghitany et al. 2012[80]	✓		✓		✓			✓	✓			Ventilation
Bryant-Stephens et al. 2009[62]			✓		✓		✓			✓	✓	
Krieger et al. 2009[61]				✓						✓	✓	
Bryant-Stephens et al. 2008[63]			✓		✓		✓			✓	✓	
Parker et al. 2008[58]				✓	✓		✓			✓	✓	
Burr et al. 2007[75]						✓						Positive ventilation fan
Kercsmar et al. 2006[76]						✓						Moisture control
Williams et al. 2006[64]			✓		✓	✓	✓	✓			✓	Professional cleaning
Eggleston et al. 2005[71]		✓			✓		✓				✓	
Krieger et al. 2005[59]				✓			✓			✓	✓	
Morgan et al. 2004[60]		✓		✓	✓		✓					
Carter et al. 2001[72]					✓		✓		✓			

Table 9. Multicomponent indoor allergen reduction interventions by study (continued)

Study	Acaricide (dust mite pesticide)	Air Purification	Carpet Removal[a]	HEPA Vacuum	Mattress Covers	Mold Removal	Pest Control	Pet Removal[a]	Laundering Linens	Cleaning Supplies Provided	CHW Education/ Instruction	Other
Htut et al. 2001[77]									✓			Ventilation; steam heating of mattress, duvet; new pillows
Warner et al. 2000[74]				✓								House-wide ventilation system
Cloosterman et al. 1999[67]	✓				✓							
Evans et al. 1999[79]					✓		✓				✓	
Shapiro et al. 1999[68]	✓				✓				✓			
Hayden et al. 1997[66]	✓		✓		✓				✓			
Carswell et al. 1996[69]	✓				✓				✓			
Marks et al. 1994[70]	✓				✓							
Walshaw et al. 1986[65]			✓		✓							Feather-based bedding replaced
Korsgaard et al. 1983[73]			✓						✓			Regular mattress vacuuming; pillows and quilts replaced; ventilation; clothes dried outdoors
Burr et al. 1980[78]									✓			Regular mattress vacuuming; quilts removed; feather pillows replaced
Total	**6**	**3**	**8**	**8**	**18**	**5**	**12**	**2**	**8**	**9**	**11**	

[a] Applied to some but not all study participants

* Not an RCT

CHW=community health worker

Acaricides

For studies of acaricides, asthma control and quality of life were not measured, while the evidence for exacerbations and healthcare utilization is inconclusive. No improvement was observed for pulmonary physiology (SOE: Moderate). For secondary outcomes, there was no improvement in asthma symptoms (SOE: High), although allergen levels were reduced (SOE: Low).

Air purification

Evidence is inconclusive regarding asthma control associated with use of air purification. Exacerbations and quality of life did not improve (SOE: Moderate), but school absenteeism was reduced (SOE: Low). Secondary measures of asthma symptoms improved (SOE: Low).

Carpet removal

For studies that encouraged removal of carpeting, the evidence is inconclusive for clinical outcomes, despite evidence suggesting reduction in secondary measures of allergen levels (SOE: Moderate). These studies did not require carpet removal, however, or stratify the results by whether this intervention was actually implemented, and therefore this component was not implemented in a standardized way across studies.

HEPA vacuums

For studies that included HEPA vacuums, the evidence is inconclusive for asthma control and pulmonary physiology measures. Exacerbations were reduced when measured as a composite of hospitalizations, ED visits, and urgent care visits (SOE: Moderate). Medication use did not change (SOE: Moderate). Two studies using the PACQLQ found improvement (SOE: Moderate) but other quality of life measures are inconclusive. Studies in pediatric populations found improvement in secondary measures of asthma symptoms (SOE: Low), but no corresponding effect was observed in studies that mixed adults and children (SOE: Low).

Mattress covers

Studies that included mattress covers showed a reduction in school absenteeism and missed activities (SOE: Low). However, no effect was observed for frequency of emergency department visits (SOE: Low), hospitalizations (SOE: High), or quality of life (SOE: Moderate).

Mold removal

The evidence for mold removal is inconclusive for most outcomes, although secondary measures of asthma symptoms improved (SOE: Low).

Pest control

For studies that used pest control strategies, measures of asthma control, medication use, and pulmonary physiology are inconclusive. There was a reduction in exacerbations when measured as a composite of multiple measures, (SOE: Moderate) but no effect was observed when hospitalizations or ED visits were evaluated as discrete measures (SOE: Moderate). Quality of life as measured by the PACQLQ improved (SOE: Low). Secondary measures of asthma symptoms were reduced (SOE: Low.)

Table 10 presents the findings and SOE for each primary active component and key outcomes.

Table 10. Strength of evidence for multicomponent interventions

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
Acaricide (dust mite pesticide) + other interventions vs. placebo	Asthma control	**Not evaluable:** Not reported in included studies.	NA	NA
	Exacerbations	**Inconclusive:** No difference in ED visits or hospitalizations in RCT of 44 mixed population. Significant reduction in hospitalizations in intervention group in RCT of 160 mixed population; no between-group comparison.	2 RCTs[68,80] n=204	Insufficient (Inconsistent, Imprecise)
	Healthcare utilization	**Inconclusive:** Significantly less use of bronchodilator or any asthma medication in RCT of 70 children.	1 RCT[69] n=70	Insufficient (Unknown consistency, Imprecise)
	Pulmonary physiology: peak flow	**No effect:** No difference in peak flow in 2 RCTs of 192 adults and RCT of 70 children. Improved peak flow reported in RCT of 23 mixed population subjects. Improved peak flow in intervention group in RCT of 160 mixed population subjects; no between-group comparison.	5 RCTs [66,67,69,70,80] n=445	Moderate (Inconsistent)
	Pulmonary physiology: FEV_1	**No effect:** No difference in FEV_1 in 2 RCTs of 192 adults and 2 RCTs of 67 mixed population. Significant increase in FEV_1 reported in RCT of 70 children. Significant increase in intervention group in RCT of 160 mixed population; no between-group comparison.	6 RCTs[66-70,80] n=489	Moderate (Inconsistent)
	Quality of life	**Not evaluable:** Not reported in included studies.	NA	NA
	Symptoms (secondary measure)	**No effect:** No difference in frequency of symptoms in 2 RCTs in 192 adults, RCT in 44 mixed population subjects, and RCT in 70 children.	4 RCTs[67-70] n=306	High
	Allergen levels (secondary measure)	**Reduced allergen:** Significant reduction in HDM allergen found in RCT of 157 adults and RCT of 70 children. Significant reduction in intervention group in RCT of 160 mixed population; no between-group comparison. No difference in allergen levels in RCT of 35 adults and RCT of 44 mixed population subjects.	5 RCTs[67-70,80] n=466	Low (Inconsistent, Imprecise)
Air purification + other interventions vs. no intervention	Asthma control	**Inconclusive:** No difference in ACT or childhood ACT score in RCT of 247 mixed population subjects.	1 RCT[57] n=247	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Exacerbations	**No effect:** No difference in hospitalizations in 2 RCTs of 1,037 children. No difference in ED visits in RCT of 937 children. No difference in "exacerbations" reported in RCT of 247 mixed-population subjects.	3 RCTs[57,60,71] n=1,284	Moderate (Study limitations)

Table 10. Strength of evidence for multicomponent interventions (continued)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
	Healthcare utilization: acute care visits	**Inconclusive:** No difference in acute care visits (not defined) in RCT of 100 children.	1 RCT[71] n=100	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Healthcare utilization and costs: school absenteeism	**Improvement:** Significantly fewer days of missed school reported in RCT of 937 children.	1 RCT[60] n=937	Low (Unknown consistency, Imprecise)
	Pulmonary physiology	**Not evaluable:** Not reported in included studies.	NA	NA
	Quality of life	**No effect:** No difference in mini-AQLQ scores in RCT of 100 children and RCT of 247 mixed-population subjects.	2 RCTs[57,71] n=347	Moderate (Study limitations)
	Symptoms (secondary measure)	**Improved symptoms:** Significant reduction in symptoms in 3 RCTs of 1,974 children. No difference in RCT of 100 children.	2 RCTs[60,71] n=1,037	Low (Study limitations, Inconsistent)
	Allergen levels (secondary measure)	**Allergen reduction:** Significant reduction for HDM, cockroach, cat, dog, and mouse allergen in RCT of 247 mixed population subjects. Significant reduction in HDM, cockroach, and cat allergen in RCT of 937 children; no difference in dog allergen. No difference in allergen levels in RCT of 100 children.	3 RCTs[57,60,71] n=1,284	Low (Study limitations, Inconsistent)
Carpet removal **+** other interventions vs. placebo or no intervention	Asthma control	**Not evaluable:** Not reported in included studies.	NA	NA
	Exacerbations	**Inconclusive**: No difference in ED visits or hospitalizations in 2 RCTs of 545 mixed-population subjects. Significant reduction in hospitalizations in intervention group in RCT of 160 mixed population; no between-group comparison.	3 RCTs[62,63,80] n=705	Insufficient (Study limitations, Inconsistent, Imprecise)
	Healthcare utilization	**Inconclusive:** Significant reduction in use of inhaled steroids in intervention group in RCT of 50 adults; no between-group comparison. Significant reduction in number of daytime terbutaline puffs in RCT of 46 adults; no difference in nighttime puffs or overall use.	2 RCTs[65,73] n=96	Insufficient (Study limitations, Imprecise)
	Pulmonary physiology	**Inconclusive:** Improved peak flow in intervention group in RCT of 50 adults and RCT of 160 mixed population subjects; no between-group comparison. No difference in RCT of 46 adults. Significant improvement in RCT in 23 mixed population subjects.	4 RCTs[65,66,73,80] n=279	Insufficient (Study limitations, Inconsistent, Imprecise)
	Quality of life	**Inconclusive:** Significant improvement in PACQLQ scores in non-randomized trial of 102 mixed population subjects.	1 non-randomized trial[81] n=102	Insufficient (Unknown consistency, Imprecise)
	Symptoms (secondary measure)	**Inconclusive:** No difference in symptoms in RCT of 50 adults and 2 RCTs of 545 mixed population subjects. Significant reduction in symptoms in RCT of 161 children. Significant reduction in daytime scores, no difference in nighttime scores in RCT of 46 adults.	5 RCTs[62-65,73] n=802	Insufficient (Study limitations, Inconsistent, Imprecise)

Table 10. Strength of evidence for multicomponent interventions (continued)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
	Allergen levels (secondary measure)	**Allergen reduction:** Significant reduction in HDM allergen levels in 2 RCTs in 96 adults and RCT in 161 children. Significant reduction in intervention group in RCT of 160 mixed population; no between-group comparison.	4 RCTs[64,65,73,80] n=412	Moderate (Study limitations)
HEPA vacuum + other interventions vs. placebo or no intervention	Asthma control	**Inconclusive:** No difference in ACT or childhood ACT scores in RCT of 247 mixed population subjects.	1 RCT[57] n=247	Insufficient (Unknown consistency, Imprecise)
	Exacerbations: composite measure based on level of care	**Reduction:** Significant improvement in composite measure of hospitalization, ED visits, and acute care clinic visits in 3 RCTs of children.	3 RCTs[58-60] n=1,509	Moderate (Study limitations)
	Exacerbations: unspecified	**No effect:** No difference in undefined "exacerbations" or "asthma attacks" in 2 RCTs of mixed population subjects.	2 RCTs[57,61] n=556	Moderate (Imprecise)
	Healthcare utilization: medication use	**No effect:** No difference in use of rescue inhaler or beta agonists in 3 RCTs of mixed population subjects.	3 RCTs[57,59,61] n=830	Moderate (Study limitations)
	Healthcare utilization and costs: school absenteeism	**No effect:** No difference in missed school days in 2 RCTs (n=583). Significant reduction in 1 RCT (n=937).	3 RCTs[59-61] n=1,520	Low (Inconsistent, Imprecise)
	Healthcare utilization and costs: work absenteeism	**No effect:** No difference in missed workdays.	2 RCTs[59,61] n=583	Moderate (Study limitations)
	Healthcare utilization and costs: missed activities	**Reduction:** Fewer days of missed activities in RCT of 937 children and RCT of 274 mixed population subjects. No difference in RCT of 309 mixed population subjects.	3 RCTs[59-61] n=1,520	Low (Inconsistent, imprecise)
	Pulmonary physiology: peak flow	**Inconclusive:** No difference in RCT of mixed population subjects	1 RCT[74] n=40	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Pulmonary physiology: FEV_1	**Inconclusive:** No difference in RCT of mixed population subjects.	1 RCT[57] n=247	Insufficient (Unknown consistency, Imprecise)
	Quality of life: PACQLQ	**Improvement:** PACQLQ score improved significantly in 2 RCTs.	2 RCTs[59,61] n=583	Moderate (Study limitations)
	Quality of life: mini-AQLQ	**Inconclusive:** No difference in mini-AQLQ scores in RCT of mixed population subjects.	1 RCT[57] n=247	Insufficient (Unknown consistency, Imprecise)
	Quality of life: CHSA	**Inconclusive:** Significant improvement in CHSA scores in pre-post study of 170 mixed population subjects.	1 pre-post[84] n=170	Insufficient (Unknown consistency, Imprecise)
	Symptoms: children (secondary measure)	**Improved symptoms:** Significant decrease in symptom days in 2 RCTs (n=1,235). No difference in symptom days in 1 RCT (n=274).	3 RCTs[58-60] n=1,509	Low (Study limitations, Inconsistent)

Table 10. Strength of evidence for multicomponent interventions (continued)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
	Symptoms: mixed populations (secondary measure)	**No effect:** No difference in 2 RCTs (n=287) in frequency of symptoms. Significant reduction in symptom days in 1 RCT (n=309).	3 RCTs[57,61,74] n=596	Low (Study limitations, Inconsistent)
	Allergen levels: house dust mites (secondary measure)	**Inconclusive:** 3 RCTs did not specify Der p or Der f; 1 found significant reduction in allergen levels, 1 found no difference, and 1 found significant reduction in both intervention and control but had no comparison. A fourth RCT found reduced Der f but not Der p.	4 RCTs [57,58,60,74] n=1,522	Insufficient (Study limitations, Inconsistent, Imprecise)
	Allergen levels: cats and dogs (secondary measure)	**Inconclusive:** 1 RCT found significant reduction in cat levels but not dog; 1 RCT found significant reduction in dog but not cat; 1 RCT found significant reductions in cat and dog in intervention group, but had no between group comparison	3 RCTs[57,58,60] n=1,195	Insufficient (Study limitations, Inconsistent, Imprecise)
	Allergen levels: cockroach (secondary measure)	**Reduction:** 1 RCT found significant reduction in cockroach levels; 1 RCT found significant reduction in intervention group but had no between group comparison.	2 RCTs[57,60] n=1,184	Moderate (Imprecise)
Mattress covers + other interventions vs. placebo or no intervention	Asthma control	**Inconclusive:** No difference in ACT or childhood ACT in 1 RCT (n=247)	1 RCT[57] n=247	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Exacerbations: ED visits	**No effect:** No difference in 2 RCTs (n=545)	2 RCTs[62,63] n=545	Low (Study limitations, Imprecise)
	Exacerbations: hospitalization	**No effect:** No difference in 5 RCTs (n=2,615)	5 RCTs [60,62,63,71,79] n=2,615	High
	Exacerbations: Unscheduled care including ED, hospital, outpatient	**Inconclusive:** No difference in 3 RCTs (n=1,181) on composite measure of unscheduled care; significant reduction in 2 RCTs (n=1,235)	5 RCTs [58,60,68,72,79] n=2,416	Insufficient (Inconsistent, Imprecise)
	Healthcare utilization: acute care visits	**No effect:** No difference in 3 RCTs (n=1,318) of unscheduled acute care visits	3 RCTs[60,63,71] n=1,318	Moderate (Study limitations)
	Healthcare utilization: medication use	**Inconclusive:** Reduced used of any asthma medication in 1 RCT (n=70); no difference in use of rescue inhaler in 1 RCT (n=247)	2 RCTs[57,69] n=317	Insufficient (Inconsistent, Imprecise)
	Healthcare utilization and costs: school absenteeism	**Reduction:** Significantly fewer missed school days in 1 RCT (n=937).	1 RCT[60] n=937	Low (Unknown consistency, Imprecise)

Table 10. Strength of evidence for multicomponent interventions (continued)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
	Healthcare utilization and costs: missed activities	**Reduction:** Fewer days of missed activities in 1 RCT (n=937)	1 RCT[60] n=937	Low (Unknown consistency, Imprecise)
	Pulmonary physiology: peak flow	**Inconclusive:** Significant improvement in peak flow in 2 RCTs (n=321); no difference in 3 RCTs (n=262)	5 RCTs[58,66,67,69,70] n=583	Insufficient (Inconsistent, Imprecise)
	Pulmonary physiology: FEV_1	**No effect:** No difference in 6 RCTs (n=1,443); significant improvement in 1 RCT (n=70)	7 RCTs[57,60,66-70] n=1,513	High
	Quality of life	**No effect:** No difference in 1 RCT using AQLQ; no difference in 2 RCTs using unspecified quality of life scales	3 RCTs[57,68,71] n=144	Moderate (Study limitations)
	Symptoms: composite symptom score (secondary measure)	**No effect:** No difference in 4 RCTs that used difference sets of symptoms to derive composite scores (n=483)	4 RCTs[57,67,68,70] n=483	High
	Symptoms: symptom days (secondary measure)	**Reduction:** Significantly fewer days reported with symptoms in 4 RCTs (n=2,368)	4 RCTs[58,60,71,79] n=2,368	High
	Symptoms: cough and wheeze (secondary measure)	**No effect:** No change in frequency of cough in 3 RCTs; reduced cough reported in 1 RCT; no change in frequency of wheeze in 4 RCTs; reduced wheeze reported in 1 RCT	5 RCTs[58,60,62,63,69] n=1,850	Low (Study limitations, Inconsistent)
	Allergen reduction (secondary measure)	**Inconclusive:** Significant reduction in Der allergen reported in 4 RCTs (n=1,305); no effect reported in 4 RCTs (n=477)	8 RCTs[58,60,64,65,67,68,70,71] N=1,782	Insufficient (Study limitations, Inconsistent, Imprecise)
Mold removal + other interventions vs. placebo or no intervention	Asthma control	**Not evaluable**: Not reported in included studies.	NA	NA
	Exacerbations	**Inconclusive:** No difference in number of urgent care or ED visits in RCT of 62 mixed population subjects.	1 RCT[76] n=62	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Healthcare utilization	**Inconclusive:** Reduced need for relief medication in RCT of 232 mixed-population subjects.	1 RCT[75] n=232	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Pulmonary physiology	**Inconclusive:** No difference in peak flow variability in RCT of 232 mixed-population subjects.	1 RCT[75] n=232	Insufficient (Study limitations, Unknown consistency, Imprecise)

Table 10. Strength of evidence for multicomponent interventions (continued)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
	Quality of life	**Inconclusive:** No difference in mean CHSA scores in RCT of 62 mixed-population subjects.	1 RCT[76] n=62	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Symptoms (secondary measure)	**Improved symptoms:** Significant decrease in symptoms in RCT of 161 children and RCT of 62 mixed-population subjects.	2 RCTs[64,76] n=223	Low (Study limitations, Imprecise)
	Allergen levels (secondary measure)	**Inconclusive:** Significant reduction in mold scores in RCT of 62 mixed population subjects.	1 RCT[76] n=62	Insufficient (Study limitations, Unknown consistency, Imprecise)
Pest control + other interventions vs. placebo or no intervention	Asthma control	**Inconclusive:** No difference in ACT or childhood ACT scores in pre-post study of 80 mixed population subjects.	1 pre-post[83] n=80	Insufficient (Unknown consistency, Imprecise)
	Exacerbations: Composite measure of urgent care	**Reduction:** Significant improvement in composite measure of hospitalization, ED visits, and acute care clinic visits in 3 RCTs of 1,509 children and RCT of 104 mixed population subjects.	4 RCTs[58-60,72] n=1.613	Moderate (Study limitations)
	Exacerbations: Hospitalization	**No effect:** No difference in hospitalizations in 3 RCTs of 2,070 children and RCT of 264 mixed-population subjects. No difference in inpatient days in RCT of 281 mixed population subjects.	5 RCTs [60,62,63,71,79] n=2,615	Moderate (Study limitations)
	Exacerbations: ED visits	**No effect:** No difference in ED visits in 1 RCT of 937 children and 2 RCTs of 545 mixed population subjects.	3 RCTs[60,62,63] n=1,482	Moderate (Study limitations)
	Healthcare utilization: Acute care clinic visits	**No effect:** No difference in clinic visits for acute care in 3 RCTs of 2,070 children.	3 RCTs[60,71,79] n=2.070	High
	Healthcare utilization: medication use	**Inconclusive:** No difference in use of beta-agonist or controller medications in RCT of 274 children.	1 RCT[59] n=274	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Healthcare utilization and costs: school absenteeism/ patient activities	**Improvement:** Significantly fewer days with activity limitations in 2 RCTs of 1,211 youths. Significantly fewer missed school days in RCT of 937 children, but no difference in RCT of 274 children.	4 RCTs[58-60,71] n=1,609	Low (Study limitations, Inconsistent)
	Healthcare utilization and costs: work absenteeism/ caretaker plans	**No effect:** No difference in missed days of work or caretaker plans changed in 2 RCTs of 1,211 children.	2 RCTs[59,60]	Low (Study limitations, Imprecise)

Table 10. Strength of evidence for multicomponent interventions (continued)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
	Pulmonary physiology: peak flow	**Inconclusive:** Significant increase in peak flow in RCT of 298 children. No difference in peak flow variability.	1 RCT[58] n=298	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Pulmonary physiology: FEV_1	**Inconclusive:** Significant increase in FEV_1 from baseline (but no comparison between groups) in RCT of 298 children. No difference between groups in FEV_1 in RCT of 937 children.	2 RCTs[58,60] n=1,235	Insufficient (Study limitations, Inconsistent, Imprecise)
	Quality of life: PACQLQ	**Improvement:** PACQLQ score improved significantly in RCT of 274 children.	1 RCT[59] N=274	Low (Study limitations, Unknown consistency)
	Quality of life: other measures	**Inconclusive:** No difference in RCT of 100 children in composite quality of life score (domains not described).	1 RCT[71] N=100	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Symptoms (secondary measure)	**Improved symptoms:** Significant decrease in symptom days or frequency of symptoms in 5 RCTs of 2,529 children. No difference in symptom days in RCT of 274 children. No difference in cough or wheeze in 2 RCTs of 545 mixed population subjects.	8 RCTs[58-60,62-64,71,79] n=3,348	Low (Study limitations, Inconsistency)
	Allergen levels: cockroach (secondary measure)	**Inconclusive:** Significant reduction in cockroach allergen in RCT of 937 children. No difference in RCT of 100 children. Significant reduction at 4 and 8 months but not 12 months in RCT of 161 children.	3 RCTs[60,64,71] n=1,198	Insufficient (Study limitations, Inconsistent, Imprecise)
	Allergen levels: mouse (secondary measure)	**Inconclusive:** Significant reduction in mouse allergen in RCT of 937 children. No difference in 2 RCTs of 398 children.	3 RCTs[58,60,71] n=1,335	Insufficient (Study limitations, Inconsistent, Imprecise)

[a]Outcomes of Asthma control, Exacerbations, Healthcare utilization, and Pulmonary physiology as defined by Asthma Outcomes workshop;[28] outcomes of Quality of life, Symptoms, and Allergen levels as defined by study authors.
[b]Study limitations derived from Risk of Bias assessments in Appendix C.
ACT=asthma control test; AQLQ=asthma quality of life questionnaire; Bla g=*blatella germanica* cockroach allergen; CHSA=children's health survey for asthma; Der f=*dermatophagoides farina* allergen; Der p=*dermatophagoides pteronyssinus* allergen; ED=emergency department; FEV_1=forced expiratory volume in 1 second; HDM=house dust mite; HEPA=high-efficiency particulate air; Mus m=*mus musculus* mouse allergen; NA=not available; PACQLQ=pediatric asthma caregivers asthma quality of life questionnaire; RCT=randomized controlled trial

Key Question 2. What are benefits and harms of using bronchial thermoplasty in the treatment of adult (>18 years) patients with severe asthma in addition to standard treatment?

Description of Included Studies

Fifteen studies were included to address the benefits and harms of bronchial thermoplasty (BT). Six trials, including three RCTs[87-89] and their 5-year, single-arm extension studies,[90-92] provided outcomes related to safety and efficacy. One of the extension studies also reported data for the control arm through 3 years. Two of the RCTs (RISA[89] [n=32] and AIR[88] [n=112]) compared BT to medical management for treating moderate to severe asthma for up to 12 months. The third RCT[87] (AIR 2 [n=288]) compared BT with sham for up to 12 months. All three RCTs were funded by the manufacturer of the Alair BT system. In the RCTs, enrollment was limited to patients who had fewer than three exacerbations within the past year and to those who did not use high doses of oral corticosteroids. To better assess the generalizability of these studies, an additional study compared outcomes of patients receiving BT as part of an RCT with those of "real-world" patients not enrolled in an RCT who were receiving BT at the same clinic as part of routine care.[93]

For additional consideration of the potential harms of BT, eight descriptive studies were included consisting of six case studies[94-99] and two case series.[100,101] Detailed evidence tables presenting information on the design of the studies, study populations, findings, and risk-of-bias assessments are located in Appendix C.

Key Points

- Patients treated with BT in one study with a sham control did not differ from patients given sham treatment in asthma control scores, as measured by ACQ (SOE: Low)
- Patients treated with BT showed greater improvements in asthma control, as measured by the Asthma Control Questionnaire (ACQ), than patients undergoing medical management without sham control (SOE: Low)
- Overall, rates of exacerbations were low, limiting our ability to draw conclusions regarding the impact of BT on exacerbation frequency. In one RCT comparing BT to sham treatment, patients experienced fewer exacerbations following BT (SOE: Low)
- Whether rates of severe exacerbations were equivalent or different between the two treatment conditions could not be determined based on one RCT comparing BT to medical management without a sham control (SOE: Insufficient)
- No difference in use of rescue medication was observed in patients undergoing BT compared with sham treatment in one RCT (SOE: Low)
- The effect of BT on health care utilization or costs when compared with medical management without a sham control was inconclusive in two RCTs (SOE: Insufficient)
- Pulmonary physiology measures (forced expiratory volume in 1 second [FEV1] and morning peak expiratory flow [PEF]) were improved in patients given BT compared to patients given sham treatment or medical management (SOE: Low)

- Quality of life scores did not differ for patients assigned to BT compared to those assigned to sham treatment in one RCT (SOE: Low)
- Quality of life scores improved in patients treated with BT compared to patients treated with medical management in two RCTs without a sham control (SOE: Low)
- The most common adverse events in patients treated with BT were bronchial irritation, chest discomfort, cough, discolored sputum, dyspnea, night awakenings, and wheezing

Detailed Synthesis

Asthma Control

Low-strength evidence from two RCTs (RISA and AIR) suggests that patients treated with BT have greater improvement in ACQ score than with patients treated with medical management (p=0.01 and p=0.001, respectively).[88,89] However, low-strength evidence in the AIR 2 trial comparing BT with sham found no difference in ACQ scores.[87] A small trial (n=25) comparing 10 patients presenting at a clinic with 15 patients from three RCTs who were treated at the same institution, suggests patients treated with BT while enrolled in an RCT saw greater improvement in asthma control than those treated with BT outside an RCT; p=0.003).[93] However, due to limitations related to the observational nature of the study design, lack of precision in the results, and unknown consistency, insufficient evidence exists to determine whether differences in patient populations factor significantly into patient outcomes following BT.

Exacerbations

Low-strength evidence from the AIR 2 trial (n=288) found that patients treated with BT had fewer severe exacerbations than patients treated with sham (posterior probability of superiority [PPS] 95.5%).[87] In the AIR 2 extension, the average decrease in severe exacerbations that required systemic corticosteroids or the doubling of the ICS dose, over 5 years, was 44 percent from baseline (baseline exacerbation rate 53.1%).[90] There was insufficient evidence from one RCT comparing BT to medical management (n=112) to determine whether rates of severe exacerbations were equivalent or different between the two treatment conditions at 12 months.[88] Rates of severe exacerbations were low, limiting our ability to draw conclusions regarding BT's impact on severe exacerbation frequency.

One RCT comparing BT to medical management found that during the treatment period (weeks 0–6), four patients treated with BT experienced seven hospitalizations due to respiratory AEs compared with no hospitalizations in patients treated with medical management.[89] In the post-treatment period (weeks 6–52), no difference was found in hospitalizations between groups.[89] In the long-term extension, BT reduced overall respiratory-related hospitalizations by 68 percent at 5 years compared with baseline.[92] When comparing BT with sham treatment, one RCT found that respiratory-related hospitalizations were increased (10.5% vs. 5.1%; PPS sham > BT=57.2%) through 12 months.[87] One RCT extension study found no difference between BT and medical management in the frequency of emergency department (ED)visits from baseline through 5 years.[92] Compared to sham, one RCT found that BT reduced the risk of ED visits for respiratory symptoms by 84% (PPS 99.9%).[87] In the long-term extension of this RCT, in patients treated with BT, ED visits for respiratory complications were reduced by 78 percent at 5 years compared with 12 months before the procedure.[90]

Healthcare Utilization

Two RCTs suggested that BT reduced rescue medication use compared with medical management at 22 weeks and 12 months.[89] Inconclusive evidence from another RCT found no difference between BT and sham in reducing rescue medication or percentage of days with use of rescue medication at the 12-month followup (PPS, 81.3% and 68.0%).[87] While use of medication is a proxy measure for true health care utilization and overall costs, self-report of rescue medication in patient diaries is an imprecise measure, and consideration should be given to the known limitation that patients do not consistently use rescue medications appropriately. Thus, although BT might reduce self-reported rescue medication use compared with medical management, the evidence base is insufficient for supporting conclusions.

Pulmonary Physiology

Three RCTs with 5-year followup and a retrospective comparative trial reported discrete spirometry data (either FEV_1 or PEF). Two RCTs and two extension studies compared BT to medical management. In the RISA trial, BT improved prebronchodilator FEV_1 % predicted compared with medical management at 22 weeks from baseline.[89] In the AIR study, patients treated with BT had greater increases in morning and evening PEF compared with medical management ($p=0.003$ and $p=0.006$, morning and evening PEF, respectively) from baseline to 12 months.[88] In both studies, mean FEV_1 values remained unchanged in BT-treated patients through the 5-year followup.[91,92] In one RCT and extension trial comparing BT to sham treatment, FEV_1 (% predicted, pre-bronchodilator) and morning PEF (L/min) improved in patients treated with BT compared with sham from baseline to 12 months (PPS 24.1% and 80.6%, respectively), and no significant change in FEV_1 occurred in BT-treated patients through the 5-year followup.[87,90] In a comparative trial, FEV_1 was similar in patients treated with BT in a clinic or in an RCT.[93]

One RCT found that BT did not improve airway hyper-responsiveness compared with medical management between baseline and 12 months (insufficient strength evidence).[88] The related extension study reported that in years 2 and 3, airway hyper-responsiveness was significantly improved compared with medical management.[91]

Asthma-related Quality of Life

There was low-strength evidence from two studies suggesting that BT significantly improved Asthma Quality of Life Questionnaire (AQLQ) scores compared with medical management at 12 months.[89] Also, in a *post hoc* analysis of a subgroup of patients (n=32) who took high-dose inhaled corticosteroids, AQLQ score was significantly improved compared with medical management from baseline to 12 months.[88] Similarly, low-strength evidence from one RCT found that patients treated with BT demonstrated increased AQLQ compared with sham in the per protocol population (PPS, 97.9%), but not the intent-to-treat population (PPS, 96.0%). However, ITT patients were more likely to gain a clinically meaningful improvement in AQLQ than sham (PPS, 99.6%).[87] In a comparative trial, no difference was observed in AQLQ between patients treated with BT in a clinic compared with patients treated with BT in an RCT.[93] However, due to limitations related to the observational nature of the study design, lack of precision in the results, and unknown consistency, insufficient evidence exists to determine whether differences in patient populations factor significantly into patient outcomes following BT.

Symptoms (secondary measure)

Low-quality evidence from one RCT suggests that BT significantly improved total symptom score from baseline to 12 months compared with medical management (p=0.01).[88] When comparing BT to sham treatment, self-reported symptom scores improved in both groups from baseline. However, there were no differences between the treatment conditions at 12-month followup, but the variability around the observed effect estimate were large. Therefore, there was insufficient evidence to determine whether symptom scores were affected by treatment condition.[87]

Table 11 below presents the findings and SOE ratings for the outcomes these studies assessed.

Table 11. Strength of evidence for bronchial thermoplasty interventions

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
BT vs. sham	Asthma control	**No difference:** ACQ scores did not differ 12 months after either BT or Sham intervention (BT: 1.31 [0.94] Sham: 1.32 [0.91])	1 RCT[87] n=288	Low (Unknown consistency, Imprecise)
	Exacerbations: severe events	**Favors BT:** Patients who underwent BT had fewer severe exacerbations per patient per year than sham (BT: 0.48 [0.067] Sham: 0.70 [0.122] PPS 95.5%)	1 RCT[87] n=288	Low (Unknown consistency, Imprecise)
	Exacerbations: ED visits	**Favors BT:** Rates of ED visits for respiratory symptoms were lower over 12 months following BT relative to sham: (BT: 0.13 [8.4% of patients] Sham: 0.45 (15.3% of patients)	1 RCT[87] n=288	Low (Unknown consistency, Imprecise)
	Exacerbations: Hospitalizations	**No difference:** Hospitalizations for respiratory symptoms at 12 month followup: BT: 2.6% of patients Sham: 4.1% of patients; Number of respiratory-related hospitalizations per patient at 12 months followup: BT: 0.13 (10.5% of subjects) Sham: 0.14 (5.1% of subjects)	1 RCT[87] n=288	Low (Unknown consistency, Imprecise)
	Healthcare utilization: Rescue medication actuations	**No difference:** Use of rescue medication at the 12 month followup: BT: 7.4 [15.01] Sham: 7.5 [12.60]	1 RCT[87] n=288	Low (Unknown consistency, Imprecise)
	Healthcare utilization: Days rescue medication required	**No difference:** % Days rescue medication used at **12 month followup**: BT: 28% [36.09%]; Sham: 29.8% [34.96%]).	1 RCT[87] n=288	Low (Unknown consistency, Imprecise)

Table 11. Strength of evidence for bronchial thermoplasty interventions (continued)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
	Pulmonary physiology	**Favors BT:** FEV_1 and morning peak flow improved in patients treated with BT compared with sham from baseline to 12 months (FEV_1 BT: 76.6 [17.74]; Sham: 79.1 [15.98]; PPS 24.1%; PEF: BT: 411.6 [110.45]; Sham: 408.7 [117.56]; PPS 80.6%)	1 RCT[87] n=288	Low (Unknown consistency, Imprecise)
	Quality of life	**No difference:** AQLQ scores did not differ in ITT patients 12 months after either BT or sham intervention (BT: 1.35 [1.10] Sham: 1.16 [1.23]; PPS, 96.0%) **Favors BT,** AQLQ improved in PP patients treated with BT compared with sham at 12 months (BT: 1.38 [1.10] Sham: 1.14 [1.24]; PPS, 97.9%)	1 RCT[87] ITT n=288 PP n= 268	Low (Unknown consistency, Imprecise)
	Symptoms (secondary measure)	**No difference:** Symptom scores improved over time in both treatment groups but did not differ as a function of treatment condition.	1 RCT[87] n=288	Low (Unknown consistency, Imprecise)
BT vs. medical management (no sham control)	Asthma control	**Favors BT:** ACQ scores improved in patients who underwent BT compared to those who received standard medical management.	2 RCTs[88,89] n=144	Low (Study limitations, Imprecise)
	Exacerbations	**Inconclusive:** Rates of severe exacerbations did not vary between treatment conditions (BT: 0.01 [0.08]; Control: 0.06 [0.24])	1 RCT[88] n=112	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Healthcare utilization	**Inconclusive:** Use of rescue medication (puffs per week) was statistically reduced in 1 small trial,[89] but not different in the other, larger trial.[88] The overall reduction in inhaled corticosteroid dose was not different between treatment groups in 1 small trial.[89]	2 RCTs[88,89] n=144	Insufficient (Study limitations, Inconsistent, Imprecise)
	Pulmonary physiology: spirometry	**Favors BT:** In 1 trial, BT improved FEV_1 22 weeks from baseline.[89] In the other study, patients treated with BT had greater increases in morning and evening peak flow compared with medical management from baseline to 12 months.[88]	2 RCTs[88,89] n=144	Low (Study limitations, Imprecise)
	Pulmonary physiology: airway hyper-responsiveness	**Inconclusive:** Airway hyper-responsiveness did not vary between treatment groups.	1 RCT[88] n=112	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Quality of life	**Favors BT:** AQLQ scores were improved in patients who underwent BT relative to those who received standard medical management.	2 RCTs[88,89] n=144	Low (Study limitations, Imprecise)

Table 11. Strength of evidence for bronchial thermoplasty interventions (continued)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
	Symptoms (secondary measure)	**Favors BT:** BT significantly improved total symptom score from baseline to 12 months compared with medical management (p=0.01)	1 RCT[88] n=112	Low (Study limitations, Unknown consistency)
BT in RCT patients vs. BT in "real world" clinic patients	Asthma control	**Inconclusive:** Although ACQ scores were significantly better following BT in patients who were enrolled in the RCTs compared to the patients from clinic, this one small nonrandomized study is insufficient for drawing a conclusion.	1 non-RCT[93] n=25	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Exacerbations	**Inconclusive:** Rates of exacerbations were low in both treatment groups and did not vary statistically.	1 non-RCT[93] n=25	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Healthcare utilization	**Not evaluable:** Data on hospitalizations and medication use not reported in a comparable manner for treatment groups.	NA	NA
	Pulmonary physiology	**Inconclusive:** FEV_1 did not differ significantly between groups.	1 non-RCT[93] n=25	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Quality of life	**Inconclusive:** AQLQ scores improved in both treatment groups but did not vary significantly.	1 non-RCT[93] n=25	Insufficient (Study limitations, Unknown consistency, Imprecise)
	Symptoms (secondary measure)	**Not evaluable:** Not reported in included studies	NA	NA

[a]Outcomes of Asthma control, Exacerbations, Healthcare utilization, and Pulmonary physiology as defined by Asthma Outcomes workshop;[28] outcomes of Quality of life and Symptoms as defined by study authors.
[b]Study limitations derived from Risk of Bias assessments in Appendix C.

ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; BT: bronchial thermoplasty; FEV_1: forced expiratory volume in 1 second; ITT: intent-to-treat NA: not available; PP: per protocol PPS: posterior probability of superiority; RCT: randomized controlled trial

Adverse Events and Mortality

Two RCTs (RISA and AIR) that compared BT to medical management reported that the most common adverse events in patients treated with BT in the few weeks following the procedure were bronchial irritation, chest discomfort, cough, discolored sputum, dyspnea, night awakenings, and wheezing.[88,89] While respiratory adverse events were higher in the AIR trial during the treatment period, rates did not differ during followup. Both trials reported 5-year outcomes in the patients who received BT in single-arm extension trials. At year 5 of the RISA extension, adverse event rates in patients treated with BT were chest discomfort (8.3%), cough

(0%), discolored sputum (0%), and wheezing (8.3%).[92] At year 5 of the AIR extension, rates of these common adverse events were bronchial irritation (2.4%), chest discomfort (4.8%), cough (4.8%), discolored sputum (0%), dyspnea (9.5%), productive cough (2.4%), night awakenings (0%), and wheezing (4.8%). Cumulatively, these studies reported that, of the 71 patients receiving BT, three experienced partial lung collapse, two developed a chest infection, and one developed pleurisy.[88,89]

When BT was compared with sham, the most common events occurring during the treatment period in those treated with BT were: anxiety (4% vs 0%), asthma worsening (52% vs 39%), atelectasis (4% vs 0%), dyspnea (11% vs 6%), hemoptysis (3% vs 0%), lower respiratory tract infection (8% vs 2%), upper-respiratory-tract infections (20% vs 11%), and wheezing (15% vs 6%).[87,102] During the treatment period, two patients receiving BT experienced partial lung collapse, one patient was hospitalized for chest infection, and one patient developed hemoptysis. In the sham treated subjects, two patients required hospitalizations during the treatment period, for worsening of asthma in both subjects.[87] In the 5-year extension that followed the BT arm, respiratory adverse events and asthma symptoms were reduced when compared to the first year. Respiratory adverse events that occurred at an incidence rate of ≥3% of patients in any of the years 1 through 5 were similar to those listed in the RISA and AIR RCTs above, and included influenza, nasopharyngitis, pneumonia, rhinitis, and sinusitis.[90]

In general, the minor adverse events reported in descriptive studies were consistent with those reported in RCTs. Serious adverse events reported in 30 patients described in five case reports and two small case series (including one published in 2006) included five cases of hemoptysis, three cases of lung collapse, and two chest infections. Additionally, one patient experienced acute respiratory failure, with severe bronchospasm, tachypnea, and lung collapse; and one patient developed a pulmonary embolism with pleural effusion, bilateral lower-extremity deep venous thrombi, shock, mediastinal hematoma, hemothorax with bleeding bronchial artery, and a pseudoaneurysm.

Finally, no deaths were attributed to BT in any of the 15 studies.

Discussion

Key Findings and Strength of Evidence

For Key Question (KQ) 1, we identified 57 randomized controlled trials (RCTs) and seven additional studies that examined seven types of interventions to reduce allergen levels in the home and improve the wellbeing of patients with asthma. Thirty-four of the RCTs confirmed that all of their enrolled patients were sensitized to an allergen that was targeted by their intervention, and an additional 11 studies reported that a majority of patients were sensitized. Sensitization was usually confirmed through skin testing. We can therefore conclude that most of the studies included patients with asthma who could have benefited from a meaningful reduction in exposure to indoor allergens.

Seven studies examined the use of acaricide as the sole intervention designed to eliminate house dust mite (HDM) allergens. The evidence suggests no difference in pulmonary physiology (SOE: Low), while other outcomes were inconclusive or not reported. Six multicomponent studies included acaricide and provide evidence suggesting no effect on pulmonary physiology (SOE: Moderate), while other primary outcomes were inconclusive or not reported. These multicomponent studies also found that acaricides reduce the secondary outcome of HDM allergen burden (SOE: Low).

Nine studies evaluated the use of air purification as a single intervention. The evidence for asthma control and pulmonary physiology measures was inconclusive, while healthcare utilization was unchanged (SOE: Low) and quality of life improved (SOE: Low). Three additional studies included air purifiers within multicomponent strategies and found insufficient evidence about asthma control outcomes. No effects were observed on exacerbations or quality of life (SOE: Moderate), however school absenteeism was reduced (SOE: Low). The secondary measures of asthma symptoms improved (SOE: Low), and allergen levels were reduced (SOE: Low).

No studies looked solely at removal of carpeting as an intervention. Eight multicomponent studies encouraged participants to remove carpets from their homes, but we could not determine from the studies how many patients actually removed carpeting, or from which rooms. Evidence from these studies is inconclusive, despite significant reduction in secondary outcomes of allergen levels (SOE: Moderate).

One small study examined high-energy particulate air filtration (HEPA) vacuums alone, but the evidence base is insufficient to draw conclusions. Four multicomponent studies included HEPA vacuums along with other strategies. The evidence was insufficient for asthma control and pulmonary physiology measures. Exacerbations were reduced (SOE: Moderate) although healthcare utilization was unchanged (SOE: Moderate) and quality of life was improved among children (SOE: Moderate). In addition, the multicomponent studies found that secondary measures of asthma symptoms improved among children (SOE: Low) but not mixed populations (SOE: Low).

Sixteen studies focused on impermeable mattress covers or other approaches designed to limit HDM allergens on bedding. The evidence suggests no difference in exacerbations, healthcare utilization, pulmonary physiology, or quality of life (SOE: High). These studies do suggest that the presence of HDM allergen was reduced significantly (SOE: Moderate). Mattress covers were also used in sixteen multicomponent interventions studies. In these studies, covers were associated with reduced school absenteeism and fewer missed activities (SOE: Low), but

no difference was found in emergency department use (SOE: Low), hospitalizations (SOE: High), or quality of life (SOE: Moderate).

Mold removal was not addressed in the single-intervention studies, but was featured in five multicomponent studies. Secondary measures of asthma symptoms improved (SOE: Low), but other outcomes were inconclusive. One nonrandomized study used pest-control strategies alone. The findings of this study were insufficient to draw any conclusions. Twelve multicomponent studies included pest-control efforts. The evidence was inconclusive for asthma control, pulmonary physiology measures, and medication use. Exacerbations were reduced when measured as a composite score (SOE: Moderate) but there was no effect observed when individual measures such as ED visits and hospitalizations were examined (SOE: Moderate). Pediatric quality of life and school absenteeism were improved (SOE: Low) as well. No studies were identified that adequately examined pet care or removal to control asthma outcomes related to pet allergens.

Inconsistency also exists between evidence of allergen reduction and improved outcomes. Many of the multicomponent studies and the single intervention studies of mattress covers found that levels of indoor allergens were reduced, with only limited evidence of resulting clinical benefits. Conversely, multicomponent intervention studies of HEPA vacuums and pest control found clinical improvement despite no significant reduction in allergens. Further complicating interpretation of the findings is that, overall, no high- or moderate-strength evidence supports consistently favorable clinical outcomes resulting from use of the above interventions intended to reduce allergen exposure.

For KQ 2, we identified three primary RCTs of bronchial thermoplasty (BT), as well as their associated followup studies. Nine observational studies also examined outcomes associated with BT. At present, there are relatively few studies examining BT in patients with severe asthma, with only two multi-center RCTs comparing BT with medical management only and one multi-center RCT comparing BT to a sham intervention.

Compared to sham treatment, the evidence suggests that BT had no effect on asthma control, healthcare utilization, quality of life, or secondary measures of asthma symptoms (SOE: Low). However, improvement in pulmonary physiology measures and a reduced risk of exacerbations were suggested (SOE: Low) when BT was compared to sham treatment. Serious adverse events attributed to BT were infrequent, and no deaths were reported.

Findings in Relation to What Is Already Known

These findings are generally consistent with previous systematic reviews of nonpharmacologic interventions for asthma. In 2011, Gotzsche and Johansen updated their Cochrane systematic review of strategies for controlling HDM exposure, including mattress covers and acaricides.[103] Similar to our review, the authors found that these interventions were not associated with significant clinical effects, and they characterized the overall evidence base as lacking necessary rigor. In 2009, Kilburn and colleagues published a Cochrane review of air-filtration devices for reducing pet allergens.[104] They identified only two relevant studies, and neither demonstrated clinical benefit. The authors concluded that the evidence base was insufficient to draw any conclusions.

A 2010 systematic review by Krieger et al. examined most of the same intervention types addressed in our review and found the evidence for some strategies to be compelling.[105] They conclude that multicomponent interventions that are tailored to a patient or family are effective. Their review also found that pest control and strategies to reduce moisture and mold were effective in both reducing mold and in reducing allergy symptoms. Reviewing many of the same

studies included in this current review, they emphasize evidence showing reduced allergen levels on home surfaces such as mattresses, floors, and carpets. They did not use GRADE methods to inform their analyses, but rather adopted a pragmatic approach that incorporated expert opinion and epidemiologic evidence drawn from noninterventional studies. While they also cite individual measures of clinical benefit demonstrated in numerous studies, we found that the evidence base lacks consistent demonstration of clinical improvement.

Similarly, our findings vary from the conclusions of the research that supported the 2007 guidelines of the National Heart, Lung, and Blood Institute (NHLBI).[1] We found that the evidence base for most interventions and most primary outcomes was low quality or insufficient, while the research that supported the 2007 guidelines found greater evidence of benefit associated with interventions to reduce indoor allergen exposure. There are several reasons that might explain the differences in our conclusions. Our review includes numerous studies published since 2007, some of which showed no effect. The inclusion criteria established for our report were not identical to the previous work, so we did not select the exact same studies even among those published prior to 2007. We also prioritized outcomes differently, which affected how our findings were organized and assessed. Our report did not assess the risk of bias of individual studies using the same instruments as the previous report, which in turn affected our analysis of the strength of evidence. Most importantly, we used the GRADE approach to evaluate the evidence base, and our conclusions were therefore shaped by the GRADE methodology. All of these differences may account for variations between our assessment of the evidence and the preceding research.

Finally, a 2014 Cochrane review[106] of BT examined the same three RCTs as we did and found modest benefits that were not clinically significant associated with BT. These conclusions are similar to our findings showing limited benefit of BT compared to medical management but not when studies included a sham control. These observations are also consistent with other systematic reviews and technology assessments.[107-109] While some outcomes may have been influenced by knowledge of the treatment condition (only the RCT comparing BT to sham was blinded), the absence of benefit for BT on asthma-related outcomes compared to sham treatment is concerning. As treatment effects were similar between BT and sham, it is unclear whether treatment response was due to a placebo effect or whether sham treatment of the lungs had a true effect.

Applicability

Several factors regarding the applicability of the evidence must be noted. Patient population is one important consideration. Current clinical guidelines organize treatment recommendations along an age continuum in which “children” are identified as patients age 11 or younger and youths greater than 12 years and adults are considered one group. However, about half the studies we reviewed for KQ 1–33 of 64 studies–include patients from both groups. This is often due to studies enrolling populations that would, in other clinical contexts, be considered “pediatric” or “adolescent” (e.g., enrolling patients age 5-15 years old). It is therefore challenging to apply the results of studies in these “mixed” populations to the discrete categories of “child” or “adult.” Given the limited robustness of most study results, however, it is unclear whether better alignment between study population age cohorts and treatment categories would result in different overall findings.

Another important consideration is the challenge of implementing home-based interventions. Many of the interventions we reviewed may be difficult for families to implement due to a range of potential barriers, including cost, language, technology, home ownership, and health literacy.

Socioeconomic status can also play a role in implementation, as can the type of living unit (e.g., house or apartment, attached or detached, single family or multifamily.) Unsurprisingly, almost half of the multicomponent intervention studies, 13 of 29, included a community health worker who received specialized training to educate patients on how to reduce home allergen exposure in a highly tailored way. Although we did not evaluate the direct impact of these health workers, as they have traditionally focused on patient education activities, their role in the process of implementing home-based strategies may be important.

Similarly, it is difficult to evaluate fidelity to proper use of a home-based intervention in the context of a study. It may be even more challenging to ensure adherence to these interventions in routine practice. Although several studies reported that adherence to study protocols was evaluated periodically (through surveys or home visits), most studies do not discuss this challenge. In clinical practice, it is likely to be very difficult to assess how successfully a patient adheres to use of an allergen-reduction strategy.

Perhaps the most significant factor in evaluating the evidence base is the interaction between multiple sources of exposure to allergens in the home and multiple strategies for addressing diverse allergens. Some of the interventions we reviewed target a single allergen, such as mattress covers for HDM, while others strategies, such as HEPA vacuums or air purification devices, address more than one allergen. Since patients vary in their sensitization to different allergens, the interplay between allergen type, intervention type, and individual patient characteristics may strongly modify the effect of these interventions. For studies examining BT's efficacy, study protocols typically restricted patient enrollment to patients who had fewer than three exacerbations within the past year and to those who did not use high doses of oral corticosteroids. Consequently, although patients enrolled in the trials had severe asthma, they were not representative of the sickest of patients. Although BT as an intervention is very different from the environmental interventions described above, important information is lacking about BT in more diverse groups of patients.

Implications for Clinical and Policy Decisionmaking

This review highlights several important considerations for patients, clinicians, and policymakers. Since asthma can significantly affect overall health and quality of life, patients and their families may be motivated to adopt interventions that are not physically invasive, such as mattress covers or air purifiers, to augment pharmacologic treatment. However, allergen-control interventions may be expensive or difficult for patients to purchase or use. Clinicians do not want patients – especially those with highly limited financial resources – to purchase interventions that are not helpful. This review raises important questions about the effectiveness of common allergen-control strategies to improve asthma control or prevent exacerbations in both children and adults.

Clinicians whose patients are potential candidates for BT may want to consider the evidence presented in this review, including the characteristics of the study populations and the outcome data presented, when determining BT's appropriateness for their patients. Available evidence suggests that people with moderate to severe asthma, who also had fewer than three exacerbations within the past year or who did not use high doses of oral corticosteroids, might expect improvements in FEV1 and quality of life. Evidence is not currently available for BT's effectiveness in sicker patients with severe asthma (e.g., those with frequent exacerbations and healthcare utilization, and substantial comorbidity), or in patients with less-severe asthma.

Limitations of the Systematic Review Process

The scope of this review may have introduced two important limitations. First, because of the breadth of interventions we evaluated for KQ 1, we restricted our inclusion criteria to studies that directly evaluated an intervention. We therefore excluded all studies that presented either: 1) observational data demonstrating an association between the presence or absence of a potential allergen source (such as a pet or carpeting) and clinical outcomes, or 2) nonclinical studies that examined the level of allergens present on a surface. This likely accounts for the lack of studies in our review addressing carpet removal and pet removal. Second, although our review encompassed a broad range of interventions for KQ 1, we did not assess some potentially relevant interventions that were outside the scope of this review, such as the growing role of community health workers in the implementation of asthma control strategies. We also did not examine the impact of interventions aimed at reducing irritants, such as second-hand smoke or dust, which may influence asthma control.

Limitations of the Evidence Base

This evidence base contains several limitations. Study size was small for many of the single-intervention studies in both KQ 1 and KQ 2, as described in the Results section. Heterogeneity of populations, interventions, allergens, and outcomes were substantial, and we therefore did not conduct any meta-analyses of study outcomes. For KQ 1, results were also frequently reported in unusable ways, such as graphically without associated text or tables or narratively without inclusion of quantitative estimates. Further, the risk of bias for individual studies was often difficult to assess because of incomplete reporting of important study characteristics such as randomization technique or blinding. A related consideration is the potential conflict of interest of studies funded by a manufacturer of an intervention (e.g., acaricides, air purifiers, mattress covers.) We identified only eight out of 57 RCTs for which the funding source had a direct financial interest in the study outcomes; however, many studies did not report a funding source and/or may have received nonfinancial support through provision of study materials.

Another important challenge is the difficulty of maintaining an allergen-reduction strategy over time. Many of the studies we included had high attrition rates, which are attributable partly to participants moving from one home to another or encountering instability in family life that may disrupt continuity. Losing patients to followup, regardless of the causes, introduces a major source of bias.

A further limitation is the inherent difficulty in evaluating the relationship between individual interventions within a multicomponent strategy. Multicomponent studies represent half of the evidence base for KQ 1, but interpretation of their results is challenging. Finally, the evidence base is limited by a lack of head-to-head comparisons between interventions. Almost all the studies we assessed for KQ 1 compared a single intervention or a bundle of interventions to either a placebo group or to no intervention. We are therefore unable to assess whether a particular intervention may be more effective than another active intervention.

With respect to KQ 2, only one of three trials was a blinded, sham-controlled trial. As seen in our evidence analysis, this study did not show similar findings to the nonblinded, medical management controlled trials. Moreover, while the RCTs enrolled patients with severe asthma, individuals with high frequency of exacerbations (>3 within the past year) were not included, limiting generalizability of the findings. One small trial was designed to compare “real-world” patients, including those with high rates of exacerbations and with no limitation on medication

use, and reported that the clinical response was lower and more variable than in the RCTs.[93] However, this study also had several limitations, which limit the weight of the findings.

Evidence Gaps

Several evidence gaps could benefit from future research. First, relatively few studies of these types of interventions exist that explicitly adopt the NAEPP framework for classifying patient populations by age categories. Future research that embraces a consistent approach to identifying "children" and "adults" will enable more standardized and robust analyses of study data. There is also a need across the board for further high-quality RCTs that add to the core evidence base. These studies could aim to isolate the effect of single interventions, especially for strategies such as carpet removal, pet removal, and pest control, which have not been well studied as individual approaches. Alternatively, they could evaluate multicomponent interventions more effectively by standardizing a set of strategies that could be tested. Head-to-head studies of interventions are also needed, which could build on the current evidence base that consists of comparisons to placebos or to standard practices. Future research could attempt to directly compare single or bundled interventions to each other. Additionally, outcomes reporting could be improved and standardized. Many of the studies we evaluated provided data that cannot be incorporated in a comparative analysis because of incomplete reporting or reliance on graphical representations of data that lack the requisite specificity. Another challenge is our limited understanding of the clinical significance of changes in many important outcomes. We need further research on the interaction between the effect size of commonly reported measures of healthcare utilization, pulmonary function, and changes in allergen levels, and meaningful clinical improvement. Finally, the methodology of studies could be reported more completely. More than half the studies we included for KQ 1 did not include important information about their methodology, introducing the possibility of risk of bias that cannot be adequately considered.

The studies for KQ 2 tended to have overall better reporting of study details, although there was lack of clarity regarding patient care, such as consistent reporting of concomitant medication use, and different trials used different measures to assess asthma control. As noted above, only one sham-controlled trial of BT has been conducted thus far. Given BT's invasive nature and the presence of a treatment effect in the sham condition, further studies using a sham comparison are needed. Studies could also be undertaken to test BT in other populations, especially patients with poor asthma control who experience high rates of exacerbations.

We also highlight the need for studies that recognize the complex set of challenges that face low-income and minority groups who have the highest morbidity from asthma. Most of the studies included in this review do not describe the socioeconomic context of their patient population, and only a few seem likely to have included a substantial number of patients living in poverty and/or inner city settings.

Similarly, it is important to better understand whether the environmental interventions studied here could directly influence health or whether they serve as markers for other influences on health that are not measured but co-exist. For example, homes that have pest infestation may be more likely to be in low-income neighborhoods where patients lack access to regular medical care, supermarkets with healthy foods, or social services, all of which may affect health in various ways that are not detected in these studies. More than half of the multicomponent intervention RCTs include a community health worker or social worker who provides education about the interventions but also link patients to a wide variety of other services. Further research on the optimal design of these community-based approaches and their impact would be useful.

We also need longitudinal studies that enable evaluation of how modifications to the home environment might have additive effects over time, or, conversely, wane in effectiveness. Most of the studies we reviewed followed patients for 6 months to 1 year. Longer-term studies could help clarify the impact of these strategies and provide insight on their sustainability over time. Similarly, research is needed into how environmental interventions in childhood affect adult health. It could be important to know whether implementation of interventions at a young age can yield greater benefits as children grow.

Conclusions

The evidence base addressing allergen-reduction interventions for patients with asthma spans 40 years and four continents and has included more than 7,000 patients. However, few conclusions can be drawn about the effectiveness of any of the interventions designed to reduce allergens in the home. For most of the critical outcomes for each intervention, the strength of evidence was low or insufficient. Moreover, results that were not rated as inconclusive tended to suggest lack of clinical effect for any of the interventions. The evidence base as a whole is insufficient to support meaningful conclusions about the effectiveness of many widely used products and strategies for improving patient outcomes by reducing environmental allergen exposure.

Three RCTs and several descriptive studies have evaluated BT. Based on the available literature, BT appears to be well tolerated and may provide benefit in FEV_1 and quality of life. The studies on BT are fairly recent and the available body of literature is small. Important limitations within the study populations limit generalizability of BT's efficacy. In RCTs examining BT, enrollment was limited to patients with severe asthma, but who also had fewer than three exacerbations within the past year or who did not use high doses of oral corticosteroids. Although one small study compared clinic patients with more frequent exacerbations and/or higher use of oral corticosteroids to patients enrolled in the RCTs, further work using methods that are more robust is needed. While BT appears safe in a highly select group of patients, no information is available regarding BT's safety and efficacy in a broader population of patients with multiple comorbidities or more severe asthma.

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Abbreviations and Acronyms

AAAAI:	American Academy of Allergy, Asthma & Immunology
AAFA:	Asthma and Allergy Foundation of America
AAP:	American Academy of Pediatrics
ACAAI:	American College of Allergy, Asthma, and Immunology
ACQ:	Asthma Control Questionnaire
ACT:	Asthma Control Test
AE:	adverse event
AHRQ:	Agency for Healthcare Research and Quality
AIR 2 Study:	Asthma Intervention Research Trial 2
ALA:	American Lung Association
APHA:	American Public Health Association
AQLQ:	Asthma Quality of Life Questionnaire
ATS:	American Thoracic Study
BCBS:	Blue Cross Blue Shield
BDP:	beclomethasone equivalent doses
Can f 1:	*canis familiaris* dog allergen 1
Bla g 1:	*blattella germanica* cockroach allergen 1
BT:	bronchial thermoplasty
CACT:	Childhood Asthma Control Test
CDC:	Centers for Disease Control and Prevention
CFC-BDP:	chlorofluorocarbon-propelled beclomethasone dipropionate
CHPAC:	Children's Health Protection Advisory Committee
CHSA:	Children's Health Survey for Asthma
CHW:	community health worker
CI:	confidence interval
CINAHL:	Cumulative Index to Nursing and Allied Health Literature
CMS:	Centers for Medicare and Medicaid Services
CENTRAL:	The Cochrane Central Register of Controlled Trials
CT:	computed tomography
DARE:	Database of Abstracts of Reviews of Effects
Der f 1:	*Dermatophagoides farina* dust mite allergen 1
Der p 1:	*Dermatophagoides pteronyssinus* dust mite allergen 1
ED:	emergency department
EPA:	United States Environmental Protection Agency
EPC:	Evidence-based Practice Center
EPR:	Expert Panel Report
ER:	emergency room
FDA:	The United States Food and Drug Administration
FEF_{25-75}:	average forced expiratory flow during the middle 25–75% portion of forced vital capacity
Fel d 1:	*Felis domesticus* cat allergen 1
FeNO:	fractional exhaled nitric oxide
FEV_1:	forced expiratory volume in one second
FVC:	forced vital capacity
GINA:	Global Initiative for Asthma
GRADE:	Grading of Recommendations Assessment, Development and Evaluation
HDM:	house dust mite
HEPA:	high efficiency particulate air filter
HEV:	high-efficiency vacuum
ICS:	inhaled corticosteroid
ICU:	intensive care unit
IgE:	immunoglobulin E
IQR:	interquartile range
ITT:	intention-to-treat
KQ:	key question
LABA:	long acting beta-agonist
LTRA:	leukotriene receptor antagonist

mcg/g:	micrograms per gram
MCID:	minimal clinically important difference
MHRV:	mechanical heat recovery ventilation
Mini AQLQ:	Mini Asthma Quality of Life Questionnaire
MUP:	mouse urinary protein
Mus m 1:	*Mus musculus* mouse allergen 1
NAEPP:	National Asthma Education and Prevention Program
NCHH:	National Center for Healthy Housing
NEEF:	National Environmental Education Foundation
NHLBI:	National Heart, Lung, and Blood Institutes
NHS EED:	U.K. National Health Service Economic Evaluation Database
NGC:	National Guideline Clearinghouse™
NICE:	National Institute for Health and Care Excellence
NIH:	National Institutes of Health
n.s.:	not significant
NR:	not reported
OCS:	oral corticosteroid
OR:	odds ratio
PACQLQ:	Pediatric Asthma Caregiver's Quality of Life Questionnaire
PC_{20}:	provocative concentration of methacholine causing a 20% drop in FEV_1
PEF:	peak expiratory flow
PEFR:	peak expiratory flow rate
PF:	peak expiratory flow
PFV:	peak flow variability
PGM3:	phosphoglucomutase 3
PICOTS:	patient populations, interventions, comparators, outcomes, timing, and settings
ppb:	parts per billion
PPS:	posterior probability of superiority
QoL:	quality of life
RAST:	radioallergosorbent test
RCT:	randomized clinical trial
RISA:	Research in Severe Asthma Trial
RR:	relative risk
SD:	standard deviation
SE:	standard error
SEM:	standard error of the mean
SGRQ:	St. George's Respiratory Questionnaire
SIP:	Scientific Information Packet
SOE:	strength of evidence
SV:	standard vacuum
TEP:	technical expert panel
TRIP:	Turning Research Into Practice database
U.K.:	United Kingdom
U.S.:	United States
u/g:	units per gram